T H E S I S

Presented for the degree of Doctor of Medicine

entitled

An investigation into the arrangement of the achromatic substance of nerve cells and of the changes which it undergoes in various forms of mental disease.

by

W. Maule Smith M.B. Ch. B. Ed. (1897) M.R.C.P. Ed.
Assistant Medical Officer,
West Riding Asylum,
Wakefield.

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All drawings were made by Camera Lucida with Leitz 1/6 objective unless where otherwise specified.

INTRODUCTION.

By reason of the greater difficulty of demonstration, the achromatic structure of the nerve cell and its relations with the surrounding tissue is still the subject of much controversey. It took a considerable time to establish its reticulo-fibrillar arrangement after its demonstration by Max Schultze in 1870. Prior to that the presence of fibrils within the cells and processes had been suspected, but this observer probably first gave an impetus to their study by reason of his work on the electric organ of Torpedo in which he was able to demonstrate the presence in the cell bodies and fibres of minute threads which he termed Primitive Fibrils. The method he employed, which consisted in mascerating the fresh tissues in a weak iodized serum, was not suitable for tracing the intracellular arrangement, but enabled him to see and describe the presence of fibrils in the nerve processes and in the cell bodies, and that the nucleus does not take part in the arrangement, but that the fibrils course over its external surface. The publication of his work gave a great stimulus to this field of research and according to Ford Robertson, the publication of Fleming's work in 1882 placed the reticulo-fibrillary theory on a more stable foundation. It was not however until 1897 when the results of Apathy's work on invertebrates were published that conviction was carried to the minds of histologists in general that the nerve cells contain a definite

stainable fibrillated substance. What Apathy did for the nerve cells of invertebrates, Bethe in the following year, did for those of vertebrates by his method which will be presently described. Since then the question of the exact arrangement of the achromatic structure, or as it is called, the neurofibrils, has occupied the attention of numerous histologists. The normal arrangements have been studied in numerous animals and in man; and even yet there are a number of questions still undecided. Experiments with a view to ascertaining the changes that follow various lesions which affect the nerve cell have been made, and observations have been carried out on Pathological material both human and comparative. As a consequence much strenuous discussion has taken place against the acceptance of the Neuron Theory elaborated by Waldeyer in 1881: and these discussions have stimulated researches in another field of inquiry viz, that of embryology, in order to ascertain whether nerve cells are developed from single units, as is maintained by the upholders of the Neuron Theory, or from multiple units as is believed in by its critics.

The present investigation was primarily directed to the study of neurofibrillary changes met with in the subjects of various forms of mental disease: but it was not long before it was found to be necessary to extend the line of investigation and to study their arrangement in the healthy state; as in a subject on which there is so much debate, a description of conflicting results by observers who frequently hold

diametrically opposite views is unsatisfactory and often misleading. It was then arranged to make a comparative study of the subject and to also ascertain the arrangement in man - and contrast the difference between human embryo and adult. I regret to say however that I have been, as yet, unable to carry out the last part of my plan because of the difficulty of obtaining suitable material, either from the human embryo or from the healthy adult. Attention has therefore been directed to various lower animals and to the changes met with in the insane.

The chief methods used have been those of Bethe and Lugaro; the former as representing the teaching of independent fibrils; the latter as representative of the teaching that the arrangement of the achromatic substance within the nerve cells is essentially an anastomosing reticulum. Other methods have been employed, notably that of Ramon-y-Cajal, described as his No. 3. method and intended by its author to chiefly show the pericellular structures.

The research has been carried out at the laboroatry of this asylum and I have had no hint or help with regard to either the choosing of the subject or the prosecution of the investigation.

hods.

These may be conveniently divided into 2 groups, 1st. Tinctorial - Bethe - Bethe-Monckeberg - Donaggio. 2nd. Impregnation - Ramon-y-Cajal, Bielschowsky, Lugaro,

In the first group and sometimes in the 2nd. the processes involve the use ofasubstance which will intensify the action of the stain. Of all substances Ammonium Molybdate is found to do this most successfully. The means by which this is done is not definitely known. Bethe explained its mordanting action in connection with his method for coloring neurofibrils on the teaching of Berthelot and Jungfleisch's law on the co-efficient of distribution: he believes that the staining depends on the amount of differentiation which takes place between the constituents of the tissue and the warm water: these two divide the Molybdenum between them. This does not imply a chemical union or interaction. Mann in his book (Physiological Histology p. 450) maintains that the mordanting action of the Molybdate salt is of a chemical nature: that the Ammonium Molybdate stands between the tissue and the dye and links the two together. It does this by having certain valencies, unsatisfied by the fibrils, and able to unite withthe dye. In connection with Bethe's original method for neurofibrillar stain he noted that the following was the order of differentiation, viz, nerve fibrils, Golgi's pericellular networks, cell plasm and nissl bodies. As a possible explanation of this sequence he adheres to the theory of Georgevics p, 331. who

supports the physical theory of staining; and according to his law dyes are carried to the tissues by diffusion and by osmosis. The degree of the intensity of the staining depends upon the osmotic pressure of the dyes in the tissues. If the osmotic pressure, to which the dye is subjected, is lowered, the number of molecules in the medium will be greater, and the dye will stain more deeply. According to the law the amount of dye in 100 grammes of tissues divided by the amount of dye in 100 c.cs. of the dye-bath $\frac{Cs}{Cn}$ = Coefficient of distribution- The dye is held in the stained substance by means of adsorption, or the power of all solid bodies to take up and retain finely divided particles into their substance. Whether the mordanting action of the Molybdenum be physical or chemical, the union is very slight and very easily displaced. Gentle heat for a few minutes either splits up the loose chemical union between the tissue and the Molybdate salt or so materially alters the physical conditions that a dissociation is produced and no mordanting follows. This is a serious drawback to the use of the tinctorial methods of neurofibrillary staining and greatly detracts from the value of Bethe's and other analagous methods. From my own experience I believe that it accounts for the feebleness, the uncertainty, and the consequent inability to form reliable conclusions from preparations prepared by methods which are so easily affected by such minute influences.

The chief methods for the coloration of the achromatic protoplasm of the nerve cells and processes are those devised by Bethe who placed the neurofibril doctrine of the nerve cells of vertebrates beyond doubt: later his original method was modified by Monckeberg, and is known as the Bethe-Monckeberg process. Perhaps the investigator who has elaborated the processes for nerve fibril coloration to the greatest degree of nicety is Arturo Donaggio. In 1896 he first published a method by which the structures were stained by methylene blue. Within the past two years he has described other methods by which he stains tissues, both in bulk and after section, by means of thionin. Altogether he describes 8 different processes which have many points in common but only differ in certain details. In all of them he relies on the use of pyridine, the subsequent mordanting with Ammonium Molybdate and the staining with thionin in very dilute solutions. Different from the foregoing processes is that of Apathy, who, with Bethe, shares the honor of first placing the neuro-fibrillary theory on a solid foundation. His work was done chiefly on tissues obtained from invertebrates; no one has succeeded to any high degree in coloring neuro-fibrils by his method in the human subject. Personally I have entirely failed with it both in tissues from the ox, sheep, pig, and man. It consists in the coloration of the fibrillary structures by means of haematoxylin-alum in the presence of salicylic acid and glacial acetic acid. The tissues are fixed in some corrosive

sublimate solution, e.g. corrosive sublimate in absolute alcohol: Picro-sublimate acetic acid or Mann's Osmium-sublimate mixture: staining is done in bulk: differentiation is carried out by means of distilled water and the tissues are embedded in paraffin. From my own experience staining in bulk by methods which require elaborated technique is not a success. Both in fresh brains of animals and those obtained from the human subject, post mortem, I confess to have failed to obtain specimens either by Apathy's method or by that of Donaggio which in any way compare with those prepared from sections. There is a want of strict differentiation, a homogeneity and an inequality of staining which is usually more intense at the periphery of the block and irregular throughout the substance.

In view of the results which Bethe claims for his method and on which he vigorously attacks the neuron theory, the present work was begun by preparing specimens after his method; the details of which are as follows:-

1st. Fix tissues, of 4-10 m.m. thickness in 3-7·5% Nitric acid for 24 hours at ordinary room temperature.

2nd. Harden for 12-24 hours in 96% alcohol.

3rd. Place in ammoniated alcohol for 12-24 hours.

The mixture consists of

Ammonia Sp.gr. 0·95 to 0·96.	1 part.
Water	3 parts.
Alcohol 96%	8 parts.

4th. Wash in alcohol 96% 6-12 hours.

5. Place in acid alcohol for 24 hours.

The mixture consists of

HCl.(sp.gr. 1·18 = 37%)	1 part.
Water	3 parts.
Alcohol 96%	8 parts.

6. Wash in 96% alcohol 10-24 hours.
7. Wash in distilled water2-6 hours.
8. Mordant in 4% solution of Ammonium Molybdate for 24 hours at 10°-15° C. for nerve fibrils and at 18°-30° for Golgi's pericellular network.
9. Rinse slices in distilled water.
10. Dehydrate in 96% alcohol: then in absolute alcohol clear in xylol, toluene, or chloroform, and embed in paraffin.
11. Cut sections 10μ thick and fix them to the slide by means of a mixture of egg white and glycerine. It is recommended not to use warm water to float the section on because of its action on the Ammonium Molybdate.
12. Fix by means of heat: dissolve off paraffin by means of xylol, wash in absolute alcohol.
13. Cover the sections on the slide by means of distilled water which should form a layer 1·5 to 2 m.m. thickness on the slide.
14. Place the sections in an incubator heated to a temperature of 55° to 60°C. and allow to remain for 2-10 minutes.
15. Pour off the water, rinse in 3 or 4 changes of distilled water, replace the slide in the oven and pour over it a solution of Toluidin Blue 1·3000

and allow to remain for 2-10 minutes.

16. Pour off excess of stain: wash in distilled water, dehydrate in absolute alcohol, clear in chemically pure benzene and mount in Grubler's neutral balsam.

Rationale of the process. The fixation in nitric acid serves to diminish the affinity of the basic dye for the granules of Nissl and the nuclei. I believe that its action is more than a simple diminution of affinity and that there is produced a complete alteration and possibly a disintegration of the chromatic substance of the cell: because if sections are treated by Nissl's process there is only a granular substance left in the parts usually occupied by the Nissl bodies. Bethe recommends the strength of HNO_3 to be between 3 and 7·5%. I used at first 3 strengths viz:- 3%, 5%, and 7·5%, in order to determine which strength was the most suitable for routine examination. It was found that the results given by fixation in the 3% solution were undecided, frequently disappointing, and almost negative. The fibrillae were more distinct after treatment with 5%: with the 7·5% solution of the acid the tissues suffered considerable damage, but when there appeared to be less tissue destruction, the cells stained well and the fibrils were well differentiated. Later on I used a 6% solution of nitric acid for fixation. The treatment with ammoniated alcohol is extractive in character and serves to remove the nucleo-proteid radical of Nissl's granules. As pointed out by Bethe if the blocks on being placed in the ammoniated alcohol solution turn

brown they should be discarded as it is a good indication that the tissues are damaged so much that further preparation of them is useless. I have been unable to determine any causal relationship between the strength of the acid and this brown coloration after treatment with ammonia. It tends to occur more frequently after the stronger percentages of acid, but this is by no means necessarily so. The correct reaction on treatment with the ammoniated alcohol should be the production of a pale yellow coloration of the grey matter. It sometimes happens that tissues treated exactly in the same way, and for the same length of time in the fixing solution give no sign of reaction on being placed in the ammoniated alcohol: the grey matter remains pale or slightly greyish in color, and the white substance has a waxy appearance. On the other hand a deep brown coloration in some cases is almost immediately produced, which indicates a destruction of the tissue. If such blocks are embedded and stained after being taken through the other parts of the process, it is found that most of the cells are practically disintegrated: in the cell spaces are little heaps of amorphous material, the intercellular substance is also granular and structureless and occasionally only is a cell preserved and stained. Such irregular results have created the opinion that the tissue itself plays a part in giving rise to them. There does not seem to be any way of checking the action of the acidon the tissue as the deleterious change is only noticed after ammoniated alcohol has been applied.

The acid alcohol aids in getting rid of the extractives of the cell and appears not to injure the tissues. The presence of the alcohol prevents appreciable shrinking of the tissue.

In arranging the sections on the slide care must be exercised not to melt the paraffin by heating the water too much. Bethe says that no warm water must be used, for the reason that the molybdate salt is washed out, but it has been my experience that gentle heat, not more than 37° C. greatly facilitates the arranging of the specimens and that it does not interfere with the Molybdate to any appreciable extent. The next stage has to be proceeded with carefully. Bethe recommends the sections to be covered with distilled water and kept at between 55° and 60° C. for 2-10 minutes. In my experience this has been too high a temperature, invariably the molybdate is almost immediately dissolved out at 56 C. or above. I have found that 45°-50° C. answers the purpose the best, below this the molybdate is not washed out sufficiently and the section after staining and mounting is found to be covered by an amorphous deposit. On an average 3-4 minutes is long enough for this stage. After washing in distilled water, the slide is replaced on the oven and the stain poured on with a pipette. The length of time the slide requires to remain depends altogether on the temperature of the oven, which as already stated, should be between 45°-50° C. The length of time required for staining is about 3 minutes: the depth of coloration increases

up to a certain point, then it becomes paler and if the section is allowed to remain longer in the oven all the stain is washed out and the section is completely decolorised. It is better to watch the staining process so that it can be stopped when the proper degree of coloration is reached. An easy way of doing this is to suck up the larger part of the staining fluid on the slide with a pipette; the stage of staining is thereby seen. By doing this 2 or 3 times at short intervals the increasing density of the staining is noted. When it has reached its maximum, the appearance of which is acquired after a little practice, the slide is at once removed from the oven, dehydrated and mounted.

I have found the use of thionin to be much more preferable to that of toluidin blue. The former is much less fickle; the latter, although at times giving beautifully stained cells, is extremely uncertain. Batches of sections from the same block have been stained well with thionin but very indifferently with the blue. Methylene Blue has also been tried but without success. The reason of this is probably that the constitution of the thionin atom is the second simplest of the series of Thiazins, and may possibly be less liable to form decomposition products.

Bethe's original process has been modified by Monckeberg and is termed the"Bethe-Monckeberg Method". Tissues are fixed in 1% HNO_3 in acetone, taken through pure acetone, acetone xylol, xylol, embedded in paraffin, and cut; the sections treated with absolute

alcohol, then acetic aldehyde in absolute alcohol, washed, stained in Bethe's toluidin blue for one hour in the cold, mordanted in ammonium molybdate, washed in alcohol and mounted in neutral balsam.
Although this process was introduced as an improvement on Bethe's original method, it is doubtful if it has served its function as such. According to Mann aceton is almost useless as a fixative for tissue. It causes great shrinking of the tissue and a disruption of any existing arrangement. For this reason he advises discontinuance of its use.

In 1904 Donaggio published an account of his pyridin methods; a very full abstract of which, by Dr Ford Robertson, appeared in the Review of Neurology & Psychiatry, September 1904. A further description of three other methods appeared in February 1905 in the same journal in a paper written by the Italian histologist. Altogether he has elaborated 8 different methods, all of which depend upon the action of pyridin on the central nervous system. This substance which is a tertiary amin with a chemical constitution $C_5N_4H_5$ of which the N has an unsatisfied affinity, acts according to Mann as a strong basic accentuator, i.e. a substance which forms a connecting link in some unexplained manner between the tissue and the stain but without participating in the union between the tissue and the stain, and consequently not acting as a mordant.

I have not had any great personal experience of the whole of Donaggio's methods but have endeavoured

to give what he describes as process 1. an extended trial, but without any degree of success.

1. Pieces of tissue 2-3 m.m. thick are fixed in Heidenhain's sublimate solution for 24 hours. Remove excess of sublimate with Iodine solution.
2. Wash in distilled water for 2-3 hours.
3. Place in pyridin for 48 hours. Change pyridin after 24 hours.
4. Attach pieces of tissue to bits of cork by means of melted paraffin, place in aqueous solution of 1•10,000 thionin for 48 hours, renew stain after 24 hours.
5. Immerse in aqueous solution 4% ammonium molybdate (to which HCl 1 m. to 1 gramme of molybdate has been added).
6. Wash in water, dehydrate, embed in paraffin; cut and mount.

The cells were unevenly stained, although the blocks were colored through and through, the nerve cells nor the pericellular network were sufficiently colored to be of any practical value.

In some of his other methods Donaggio makes use of pyridin as a fixitive and hardening agent as well as an accentuator, with good results.

But of even greater importance than the tinctorial methods for neuro-fibrillar staining, are those processes by which there is an impregnation of the fibrillae by means of metallic silver: the principles of the various methods by which this is accomplished depend on those of photography. The four outstanding names associated with the methods are Ramon-y-Cajal, Bielschowsky, Lugaro and Ford-Robertson.

which appeared in December 1903.

The principle of Ramon-y-Cajal's original method which consisted in the fixation and hardening in silver nitrate was the reduction of the silver by formol and pyrogallic acid. The method tended to obscure the structure of the greater part of the block; the peripherial parts were so much overstained as to obscure the structural arrangements altogether, only small areas of the section could be studied: the action of the silver nitrate on the fresh tissues also tended to produce skrinking. Early in the following year improvements were suggested and adopted and 3 processes were elaborated. (1) For myelinated axis cylinders. (2) Nonmyelinated axis cylinders and neurofibrils. (3) For pericellular networks chiefly. Methods 2 and 3 are practically similar. In 2. the pieces are hardened in 96% alcohol and ammonia a few drops to 1.c.c. for 24 hours. In 3. the hardening agent is commercial formal 25.c.cs. Distilled water 100c.cs. Ammonia up to 1.c.c. for 24 hours. The remainder of the methods are similar.

3. Wash in water - in case of formol hardening for 6 to 12. hours

4. Immersion in 1½% solution of $Ag\ no_3$ in an oven heated to 30° -35° C. for 3 to 5 days.

5. Reduction in solution of formol 5c.cs.
Acid pyrogallic 2 grammes. } 24 hours.
Distilled Water 100 c.cs. }

6 Wash in water.

7. Imbed in celloidin and cut.

I have used No. 3 method for the demonstration of the pericellular network. It serves to show the structure fairly distinctly especially in the cerebellar cells, but there is a want of contrast in the structures, This is remedied to a great extent by the use of a gold toning bath as was pointed out by Lenhossek who used the bath recommended in Bielschowsky's process. In searching for a method which would afford a greater tissue than contrast ~~to~~ the original I used a bath of Ammonium Sulphocyanide 2% and gold chloride 2% ā ā 12c.cs. water to 100 c.cs. Immersion in this for 5-10 minutes then fixation in Hyposulphite of Soda 2% solution removes the brown color of the Cajal preparations and substitutes a rich plum colored background in which the pericellular network is well shown. Instead of embedding the blocks in celloidin or collodion as originally recommended by Ramon-y-Cajal, I use the paraffin process; dehydrate gradually from 50% methylated spirit, pure spirit, 60, 70, 80, 90% to absolute alcohol and clear in chloroform.

About the end of 1903, almost simultaneously with the appearance of the description of Ramon-y-Cajal's method, Bielschowsky published the details of his process. The principle involved is the slow reduction of ammoniated silver nitrate by means of formaldehyde. The tissues are fixed and hardened in formol, cut, and the sections soaked in silver nitrate, treated with ammonia, replaced in formol, treated with a weaker solution of silver nitrate and ammonia, toned in an acid gold bath, dehydrated, cleared, and mounted in balsam.

The end in view is a reduction of the ammoniated silver nitrate by means of alkaline formalin; and a selective deposition of the silver on the nervous structures. It is agreed by most workers that this method is one of the best which have yet been described for the demonstration of the cellular networks. It traces out the intracellular fibres, the medullated and non-medullated nerve fibres and the nets of Golgi with great distinctness. One great drawback to the use of it is that it stains very prominently structures other than nervous, e.g. fibrillar connective tissue, glia cells, and even the Nissl bodies. The different manipulations carried out with sections, to a great extent prevents the deposit of silver products which in blocks it is scarcely possible to prevent, and it also more nearly assures an equal deposition through the whole section so that this inequality present in blocks is avoided.

In July 1904 Dr Ford Robertson described a process which is applicable to tissues in block. It is essentially a modification of Bielchowsky's method. Dr Robertson thinks that the unevenness of impregnation can be avoided by washing out the formalin before placing the tissue in the nitrate of silver bath; a special reducing bath of formalin after the tissues are removed from the ammoniated silver nitrate is not necessary. The blocks are kept in the dark when in the silver bath, which is allowed to act from one to 10 weeks. The process requires the tissues to be cut by freezing: the sections are washed in ammoniated water, and toned in an acid gold bath. Ford Robertson

claims for his method that it is capable of very general application in normal and pathological histology; that it demonstrates the neurofibrils in their extracellular and intracellular course, and occasionally the buttons of Auerbach are shown. In many respects however, the method of silver coloration elaborated by Lugaro, published by him towards the end of 1904 and epitomized by Ford Robertson in April 1905, is preferable to any of the former. It is a modification of Jorē's colloidal gold method. Lugaro employs colloidal silver and tones in a gold chloride bath: he claims for his method that the neurofibrils are deeply stained and can be followed in their course, whereas with colloidal gold the fibrils are faintly tinted, indistinct and cannot be followed.

A tabulated list of the steps of the method is appended.

1. Tissues 5-10 m.m. thick are fixed in a mixture of 6% pure nitric acid and 10% formolin, equal parts, for 24 hours.
2. Wash shortly in water.
3. Transfer to ammonium molybdate solution which should be 5% strength. Allow to remain 24-48 hours. The shorter time for the large nerve cells; the longer if the smaller cells are to be studied.
4. Wash shortly in water.
5. Dehydrate rapidly in 90% and absolute alcohol: clear in chloroform, embed in paraffin.
6. Thin sections are fixed on albuminizes slides, by means of heat; the paraffin is removed with chloroform, then the absolute alcohol, and the section is washed

in distilled water. This last washing is recommended to be very thorough, the tissue to remain in the water from 2 to 24 hours.

7. The slides are put into collargol solution of 4% strength and allowed to remain from ½ to 1 hour.
8. Wash in distilled water; place in bath consisting of 2% gold chloride 1 part: 2% ammonium sulphocyanide 1 part: distilled water 8 parts. Keep the fluid in motion until the section assumes a grey or violet tint.
9. Fix in hyposulphite of soda solution (optional).
10. Dehydrate, clear in xylol and mount in balsam.

Lugaro claims for the process that the intracellular network is exclusively stained; that the medullated and non-medullated fibres are unstained: that the axis cylinder is colored up to its myelin coat.

This method is a very valuable one for the study of the neuro-fibrils within the nerve cell bodies, and larger processes. The results are uniformly good, even the smallest cells can be stained, the differentiation is excellent; but there is a great drawback to its general application. Colloidal silver is an unstable product; it comparatively quickly undergoes change and looses its power of staining. Even different samples of the substance vary in their degree of stability. The substance has to be kept in the dark and in a cool place. I think that much heat may sooner lead to its breaking up. The most reliable samples are said by Lugaro to be got from Heyden di Radibeul of Dresden. When used fresh this substance shews a wealth of fine fibrils within the cell body

which are not shown by any other method that I am acquainted with. In using it I prefer to leave the sections in the silver solution overnight as I believe by so doing the fibrils are more deeply stained. In using the gold bath I have found that after the usual slaty grey color appears, if the sections are removed from the bath, covered by a thin layer of the gold solution and allowed to slowly dry, the background of tne section assumes a beautiful rose color which forms a very much more striking contrast than the grey background. It is practically always necessary to fix in hyposulphite of soda 2% solution; it removes any silver deposit that may have been thrown down during the manipulations. Practically all the sections which I have prepared show the medullated fibrils stained. In the spinal cord so much is this the case that many of the sections look like very successful Weigert Pal preparations.

Intracellular Fibrillary Arrangement.

The position occupied by the neuro-fibrils in 1900 was well described by Dr Ford Robertson in his text book on the pathology of mental diseases. Up to that time the fibrils had been studied by Delafield's haematoxylin and Heidenhain's iron haematoxylin, but these methods had been replaced by the more perfected methods of Bethe, Apathy, and Donaggio. As yet however the latter observer was using his methylene blue method of 1896. The descriptions of Bethe and Apathy were chiefly followed. In brief these were for the larger cells as follows. A certain number of the fibrils run through the apical process, cell body and basal dendrites; a few pass from dendrite to dendrite: the fibrils are more numerous in the apical process, less numerous in the cell body and least numerous in the dendrites. The majority of the fibrils from the apical process form a reticulum within the cell body round the nucleus- the deep or perinuclear reticulum. More superficially the fibrils are independent and pursue a free course as described. The axis cylinder arises from the perinuclear reticulum which becomes arranged into independent fibrils much finer in calibre than those of the dendrites: A certain number of the coarser dendritic fibrillae pass into the axis cylinder.

Donaggio by means of his methylene blue method, which he described in 1896, never quite accepted Bethe's teaching with regard to the independence of the neuro-fibrils and in 1903 he described fully the endocellular arrangement of the fibrils as shown by his method.

He maintained that the nerve fibrils form a dense network inside the cell, that the network is much more dense round the nucleus, that the fibrils are not independent and that the appearances produced by Bethe's methods are due to incomplete staining.

Rossi, who worked with a special gold process of his own and studied the neurofibrillar arrangement in the cells of the spinal ganglia and spinal cord confirms Donaggio's findings with regard to the endocellular reticulum: he describes the cells as having an investing membrane of granular layer, an endocellular reticulum of finer meshes at the nucleus and a more open network at the cell periphery; that the meshes contain deeply stained granules and that from the peripheral granular zone fibrils stream away to the surrounding tissues.

Soukhanoff described an endocellular network which was chiefly perinuclear and did not reach the cell periphery: he also thought that the significance of the appearances indicated a system of intracellular canaliculi. In a later paper he thinks that the network described by him is not the same as that described by Donaggio but is analagous to the intracellular spaces or Etat Spirematеux of Nelis.

In 1904 Ramon-y-Cajal maintains that his method not only stains Bethe's fibrils but also the fine connecting bands which unite them. This is confirmed by Weiss and Azoulay who maintain there is a network in place of parellel fibres. Soukhanoff also thinks

the intra-cellular network described by him greatly resembles that described by Golgi.

Marinesco, employing Ramon-y-Cajal's methods also confirms that Author's observations with regard to the endocellular fibrillary arrangement. He describes a superficial and a deep network which are distinct at the cone of origin of the axis cylinder but which unite when it becomes the axone. In cells of the elongated fasiculated type the fibrils pass through without anastomosing but Marinesco believes that there are lateral connections. He describes two kinds of fibrils.

1. Those that do not loose their indivuality.
2. Those that break up completely within the cell body.

The spinal ganglia and Purkinjes' cells are distinctly reticular.

Donaggio in a paper published in the latter end of the year, describes his perfected new methods. He uses pyridin as a fixing and hardening agent and stains with thionin. He alters his position somewhat and describes 2 kinds of cells,

1. Those with endocellular reticulum only.
2. Those with(A) Endocellular reticulum and (B) fibrils coursing through the cell and maintaining their indivuality.

He declines to express an opinion regarding the anastomosis of the long fibrils. He thinks that Cajal's methods are in some respects unsatisfactory and believes that they fail to stain such fine fibrils as is ppossible with his own thionin methods. He

thinks the pericellular reticulum is neuroglial but that there are ray like processes in the meshes of the reticulum which might be nerve endings. In February 1905 he described in detail the mode of origin of the axis cylinder. Within the cell the fibrillary network forms layers of condensation which is characterised by the smaller mesh of the network. The principal ring is that which surrounds the nucleus and he terms it the perinuclear ring.

In some animals, e.g. the rabbit, the other areas of condensation are distinctly made out. In man, the dog and cat, they are not so obvious.

The axis cylinder is said by him to take origin from 4, 5, or more different parts of the cell.

1. From the periphery of the cell reticulum.
2. From the thickening of the reticulum which is not perinuclear.
3. From the deeper portions of the cell and fibrils from the level of the nucleus.
4. Reticulum round the centre of the cell.

With regard to the independence of the long fibrils he does not express an opinion, but Rossi and Michote think that all the fibrils form the internal network. Much support is also given to this by Lugaro, who uses his colloid silver method for which he claims perfect staining of the most minute endocellular fibrils. Lugaro also maintains that the axis cylinder is composedof lozenge shaped meshes which are closely appressed and so produce an appearance of fibrillation. He strongly maintains that there are no independent

fibrils in either axis cylinder or cell body.

With regard to the functions of the differently constituted cells Donaggio suggests a theory. He thinks that those cells which only have an endocellular reticulum have only one function, viz., that impulses are conducted in one direction, and the reticulum is an apparatus for reception and synthesis of stimuli transmitted by cellulipetal paths. In the case of the second class of cells described by him - those which in addition to the endocellular network have long fibrils, there are two systems:—

The long fibrils pass through to the axis cylinder, and might conduct impulse cellulifugally: whilst the reticulum within the cell receives the cellulipetal impulses.

PERSONAL INVESTIGATIONS.

I have used material obtained from the ox, pig, sheep and cat; and have employed the methods of Bethe, Lugaro and Ramon-y-Cajal No.3. The two former methods were employed as representative of two schools of teaching; the first named observer maintains that the fibrils course through the cell without anastomosing and as a result the cell has a fibrillated appearance while the other maintains that there are no free fibrils, but that there is a network formed in the cell body in which all the achromatic threads from the processes anastomose.

The appearances presented by the cells from various parts differ considerably in the fibrillar and reticular arrangement. The ganglionic cells of the cortex have a much greater fibrillated appearance than those in the medulla or cord; this is well seen in preparations by Bethe's method. Further more the arrangement of the fibrils in the ganglion cells of the cortex differs from that in the smaller cells. Before going into minute comparisons it might be said that my findings with regard to Bethe's method confirm in general the criticisms of others. In well stained cells the fibrils are most distinctly brought out, and as they lie in the processes many of them appear quite distinct; and in some cells a few are seen to pass completely through the cell body and into the axis cylinder process or basal dendrites. The interfibrillar structure in the fibrils is homogeneous and often no fibrils are seen in its substance. In the cell body however there is often

seen very minute processes and fibril network. In the examination of sections however it is evident that the process even in its most successful preparation stops short of giving fully stained specimens, and thus of conveying appearance to the structural arrangements within the cell, which are imperfect. This arises from the fact that sometimes there are traces of fine fibrils passing between the prominent larger neuro-fibrils; and I am unable to agree with those writers who maintain that Bethe's method does not show these finer structures. In the cell body itself there are often seen appearances almost exactly corresponding to Donaggio's figures illustrating the short and long fibrils and the perinuclear condensations. The cells in the spinal cord do not show any independent fibrils in the cell body but in the processes the fibrillae are always seen and have the same characteristics as in the cortical cells.

Lugaro's colloidal silver method shows very much greater wealth of finer meshwork both in the nerve cell bodies and in the processes. The disadvantages of the method have already been discussed. Lugaro believes that it is a specific st/ain for the endocellular networks and that it is complete. At its best I am prepared to agree with this view, as [redacted] the remarkable detail of structure clearly shown in the cells and its definite arrangement carry strong conviction with them. For some unexplained reason however the preparations from the motor cortex of the lower animals do not show the sharp differentiation and the depth of fibril staining which might be expected from a comparison with

sections from the human cortex. As a general rule the cell structure is much fainter and the networks not so uniformly colored especially round the nucleus. I can only offer a possible explanation of this by suggesting that the tissues were placed in the fixing agents before actual cell death occurred and before the molecules of the cell plasm had time to become consolidated post mortem as was advocated by Gierke, who maintained that living tissues in which metabolism is going on do not stain; that nearly dead tissues stain fairly well and that tissues which are quite dead become colored best. This would explain my findings, as in pieces removed from a pig and cat and put immediately after death into the fixing agents, the results are not satisfactory: the cells of the medulla of the pig and of the cerebellum of the cat are most varied. Many of the cell groups of the former animal are minutely stained; others are scarcely colored. In viewing the results obtained by Bethe's method this has to be kept in mind and may serve as a possible explanation of why this stain is so frequently seen to stop short at the perinuclear structures as is very frequently seen in the sections from the lower animals.

The small and large pyramidal cells present a somewhat simpler endocellular arrangement than the layer of giant cells, especially by Lugaro's method, there is an anastomosing fibrillated structure seen in the cells; it is however indistinct; the fibrils are much fewer and the endocellular networks are less elaborate. The giant cells and the higher differentiated pyramidal cells mentioned by Alfred Campbell present

wellmarked fibrillation of the apical process: in the preparations by Lugaro's method the fibrillation is more wavy and appears to be produced as that observer maintains by lozenge shaped reticular spaces being crowded together. In the cell body the spaces seem to become separated from each other - the more superficial expanding more and consequently giving rise to larger peripheral spaces: to less large spaces which form the intermediate zone; and to an internal zone situated immediately round the nucleus, composed of still smaller meshes and forming the perinuclear ring.

The exact manner in which the axis cylinder process arises from the nerve cell bodies is unsettled. There appears at its zone of origin what seems to be an area of finer meshed reticulum formed by fibrils streaming from the apical process over the nucleus toward the base of the cell. I believe that it is generally thought that the fibrils here undergo a rearrangement from which arise the fibrils which pass as the axone. From the preparations which I have examined there does not appear to be an actual rearrangement. The fibrils in their course from one pole of the cell to the other are interrupted by the interposition of the nucleus; they are pushed aside. The peripheral zone clings to the cell wall; the fibrils of the intermediate zone stream round on either side and form an anastomosis at the base of the cell among themselves and the adjacent zones. All the mass of fibrils are on their way to the sheath of the axis cylinder. The large meshes of the peripheral zone

become pressed together until they resemble fibrils: those forming the middle and perinuclear zones are more nearly opposite the entrance to the axis cylinder and consequently become less and less altered as a line direct with the process is reached. In this way a cone is formed, with the base situated at the base of the cell and the cone gradually extending up until its tip may reach the perinuclear ring. It can in this way be easily seen why there are apparently independent fibrils streaming through from the apical process to the axis cylinder. The basal dendrites probably arise in a similar manner from the peripheral zone, and this would serve to explain the appearance of fibrils passing from the basal processes to the axis cylinder.

I regard Bethe's method as being useful for showing the general arrangement of the neurofibrils in the cortical cells, and Lugaro's method as an excellent one for supplying the details which the process of the former do^es not reveal.

In the human subject the cells which have been examined and which appear to represent a normal condition there is a very much greater wealth of endocellular network which has a general arrangement similar to that already described. But I have observed that the axis cylinder has a much greater area of origin; that it usually arises from all three layers of endocellular condensation; and that in diseased conditions which will be described later, the connections with the perinuclear ring are the last to be destroyed.

The dendrites can be followed through the perinuclear nets in to the peripheral zone. The former structures are sometimes distinctly seen by the method of Lugaro and will be again referred to.

The cells of the medulla and spinal cord very closely resemble each other. The general arrangement also of the intracellular network bears a close resemblance when treated by either process. The amount of detail however is much greater in the cells treated by the colloid silver method. In almost every case there is a well marked 3 layered arrangement of the endocellular network which resembles in its general characters that found in the cortical cells. That is to say, the meshes are wide and well marked at the periphery, intermediate in size in the middle zone and much smaller to form the perinuclear ring. Donaggio has described various condensations of the endocellular network besides the perinuclear ring: but I gather from his descriptions that these condensations are variable in their positions and interrupted. The sudden transition between the meshes of the external and middle layers causes such an appearance as Donaggio describes.

Fig.4. is taken from the medulla of a pig and is prepared by Lugaro's method. The 3 layers of endocellular fribrillary condensation are well seen, especially is the perinuclear ring prominent.

Fig.3 is taker from the lumbar cord of an ox and is prepared by Bethe's method. It shows the 3 layers of condensation well defined; but the meshes are larger; the detail is not so full, and the perinuclear ring

is much narrower.

The arrangement of the fibrils in the processes is clearly shown in Lugaro's preparations to be , for the most part, a network: the individual fibrils anastomose freely. The description given for the processes of the cortical cells is applicable here also. Whether these anastomosing fibrils are to be described, has some have done, as secondary fibrils, is questionable. They do not always appear to greatly differ in thickness from the primary fibrils and the disparity in size may in some cases be due to the orientation. Bethe's method does not reveal them, and that fact might be urged as proof of their finer structure. The interfibrillar substance by his method is a homogeneous structure with no fibrils.

By both methods the fibrillar structure at the entrance to the cell body is replaced by a reticular arrangement, which I believe to be similar to that already described for the cortical cells.

In the case of Fig. 4. there is an illustration of an apparent fibril which is really produced by the close application of reticular meshes. It is a curious fact that the specimens prepared by Bethe's method do not show any apparently independent fibrils: these seem all to enter the reticular formation.

The origin of the axis cylinder is less distinctly apparent than in the cortical cells. It is indicated by the larger meshes which are prominently seen in both drawings. I do not consider however that the endocellular network undergoes any actual rearrangement; but that the origin described for the cortical cells

is probably applicable here also.

As regards the cerebellar cells the method of Lugaro serves to demonstrate the fibrillar structure of the processes and the reticular formation of the cells. I am led to think however that here the method is not so precise as in other situations. Compared with the method of Golgi, the colloidal silver process falls very far behind in the demonstration of the wealth of connections of Purkinjes' cells. The larger trunks as shown in Fig.5. are well seen and also the arrangement within the cell body; but unless the terminal processes of these cells are different in composition to the other parts, this method is not adequate from which to draw conclusions.

The basket arrangement around each cell is very faintly and indistinctly represented; but the structure being pericellular may account for its want of demonstration.

PERICELLULAR NETWORK.

Although this structure was first described by Golgi as far back as 1882, and although it has received the attention of numerous investigators since that time, the question of its composition has not been definitely settled. Up to 1896 the methods employed for its demonstration were those of Golgi and modifications of his original process. Up to then the fibrillar structure of the achromatic protoplasm of nerve cells had not been universally accepted and methods for the demonstration of endocellular networks were only then commencing to be elaborated. With the methylene blue method of Donaggio published in 1896, the method of Bethe, the later silver methods of Ramon-y-Cajal, Bielschowsky, and the more perfected methods of Donaggio, the nature of the pericellular structures have been more definitely settled.

There are 3 views held as to their composition: some maintain that they are nervous elements whilst others believe them to be of neuroglial origin, and others think they are artefacts.

They are stained by practically all the methods employed for the demonstration of the achromatic protoplasm. By the aid of his well known sublimate impregnation method, Golgi was able to describe a reticular arrangement round the cells and suggested it to be of the nature of neuro-keratin: in 1898 he described it more fully: he says it is free from the cell body, it is very fine, reticular, delicate, homogeneous or striated, has uniform round meshes and

covers the cell body and processes.

Prior to 1898, Martinotti had described a fine reticulum which he also thought to be of neurokeratin; his description partly resembles that of Golgi but he believed that the homogeneous membrane of anastomosing fibrils transmitted from its inner surface, fibrils, which passed to the unstained portions of the cytoplasm: he did not think it enveloped the axis cylinders: he looked upon it as an isolating body. Bethe found that his method for neurofibrils also colored the pericellular reticulum: he described it in various groups of cells but not in those of the spinal ganglia. He believed the reticulum to be formed by the terminations of the axis cylinders of nerve cells and that it establishes continuations with the neurofibrils of the cytoplasm. This view is not supported by other observers. Ramon-y-Cajal thinks that there is no reason for believing that there is a real pericellular network. In this Lugaro is inclined to give his support. The figures that have been described by Golgi and others, as composing the network, are simply due to the coarser meshes of the superficial layers of the spongioplasm, and that it has no connection with the nervous elements around. Marinesco in a paper published in 1904 supports the view that the structures are artificial and this is agreed to in a paper published in the same year by Lugaro. Van Gehuchten thinks the presence of a network is doubtful; but that if it exists it takes no part in the functions of conduction.

Perhaps the view advanced by Donaggio that the plexus is a demonstable structure, that it is in close relationship to the nerve cells and probably forms anastomosis with these cells; but that it is of neuroglial origin and consequently has nothing to do with nerve cell function as that is usually understood, is the theory that finds the most favour at the present time. In 1896 Donaggio described a structure stained by means of his methylene blue method, which he regarded as belonging to the achromatic protoplasm and to be similar structures to those described by Nissl, Ramon-y-Cajal, Semi Meyer, Aldren Turner and Hunter. On the publication of Ramon-y-Cajal's paper in 1904, Donaggio supported his assertion that there was no isolating investment but that there are peripheral connections which are neuroglial and not nerve fibrils. Ford Robertson supports this view and maintains that the structures shown by Aldren Turner and Hunter by their intravitam methylene blue method are distinct from the network described by Donaggio and that the two are coexisting structures.
In a paper published in 1905 Donaggio still maintains the neuroglial nature of the pericellular reticulum, and is more certain that the anastomosis which it forms is of neuroglial nature. Held, who formerly believed the structure to be nervous, now accepts Donaggio's view. In the meshes of the pericellular reticulum are minute, ray-like structures which stain by Donaggio's method and which are composed of a single centre which does not stain and numerous fibrils which radiate out from it. "Radiations" or "Raggiere"

is the term that has been given to them by the author. Held confirms the presence of these minute structures and believes that they are the same as the structures described by him under the name Sternformigen Haufen. The significance of these minute bodies is not settled: Held believes them to be of nervous structure: Donaggio does not commit himself to an opinion: Ramon-y-Cajal suggests that the central unstained portions correspond to the buttons of Auerbach which are impregnated by his silver methods, and which are not colored by Donaggio's method. The question of their function and connections are, however, not understood.

The findings of Fragnito, Cupobianco and Paladino give support to the views of Donaggio regarding the neuroglial origin of the network. In studying the development of the nerve cells the former observer states that glia fibrils pass into the cell body as far as the nucleus . He thinks that the fibrils correspond to those of the neurospongium which with vessels and lymphatics lie amongst the neuroblasts when these are undergoing development into nerve cells: he prefers this view to that which suggests that the fibrils penetrate the cell body after it is fully developed. Sciuti also from a study of the reticular formation and development comes to the conclusion that it is neuroglial.

DO NERVE CELL FIBRES ANASTOMOSE ?.

The question of the exact mode of termination of the nerve fibre in relation to adjacent cells has exercised much attention since the introduction of Golgi's method. Since the study of the neuro-fibrillar arrangements in the nerve cells has been so fully described by means of the various newer histological methods, more attention has been given to the question of anastomosis.

Golgi himself thought that the axis cylinder broke up into a network round the adjacent nerve cells: Vassale and Donaggio suggested that there might be an anastomosis between the gemmulae of the protoplasmic prolongations of one cell and the axis cylinder of another. In the cerebellum Hill thought it possible that the axis cylinders of the granule cells ended in the gemmulae on the protoplasmic prolongations of Purkinje's cells. Held believes in the continuity of the axis cylinder and adjacent cell processes. On his elaboration of his neurofibril method, Apathy demonstrated that in invertebrates the primitive fibrils may run through several ganglion cells and form numerous anastomosis: he maintained that each primitive fibril consists of numerous elementary fibrils and the whole mass is one continuous sheet of connections. Bethe agreed with Apathy's views of anastomosis in the intercellular reticulum. Ramon-y-Cajal does not consider that there is continuity but believes that there is contiquity between the nerve cells and fibres; that the chalices described by Held

envelope the cells but do not penetrate them .
Veratti does not believe there is continuity but that the chalices described by Held are products of partial impregnation of a membrane which surrounds unipolar cells.

By means of his newer processes Ramon-y-Cajal has been able to describe structures on the cell body which he terms the "Buttons of Auerbach". They are black, often granular bodies, the centre is sometimes clear: they are very abundant on the cell bodies and processes of the cells of the spinal cord and bulb; they have not yet been demonstrated on the cells of the cerebral cortex. Van Gehuchten thinks that these buttons of Auerbach end always independently on the cell body, they do not form a network and are the same as the structures described by Held and named by him Endfusse. The suggested relationship of these structures with the Radiations of Donaggio has been already noted.

A detailed description of the nerve fibre terminations in the cells of the accoustic centre was given by Donaggio in 1903. The ventral nucleus contains certain unipolar cells which have only one process - the axis cylinder - which ends in the Corpus Trapezoideum. These cells have a pericellular basket which is known as the accoustic terminations of Held and which he supposed to be formed by adjacent nerve fibres. Veratti thought that the appearances were due to the incomplete staining of the cell membrane and that the fibrils were really the axis cylinders of the cells. Donaggio was able to show that the axis cylinders and the large nerve fibrils are distinct.

The fibrils forming the large nerve fibres, break up into bundles, and at some distance from th cell they divide and subdivide. Some are inserted into the peripheral cell zone, course in this for some distance, and become continuous with the endocellular fibrillar apparatus: others pass straight across the peripheral clear zone to the endocellular fibrils. Donaggio is of opinion that the accoustic terminations of Held are not really nerve fibre terminations but are part of a fibrillar conducting apparatus.

DEVELOPMENT OF NERVE CELLS AND FIBRES.

It is necessary before considering the functional activity of the nerve cell to review the work that has been done by the several investigators within recent years on the development of the nerve cell and its fibres. At the present day there are two established theories of origin and these are:-

1. That the nerve cell and its fibres are derived from a single unit.
2. That the nerve cell and its fibres are formed from a number of units.

The former may be called the monocellular, the latter the pluricellular origin of the nerve cells.

The monocellular theory is the more established, and until quite recent years was generally accepted: according to it each nerve cell is derived from a single germinal cell. These germinal cells are numerous at the 4th. week of embryonic life and occupy positions at the deepest parts of the neural tube in

the intervals between the columnar epithelium. At the 4th week they are without processes, but as time goes on they migrate in an outward direction and proceed to take up the positions they ultimately occupy in the grey matter of the cerebral cortex and spinal cord; they become pyriform and are termed neuroblasts; the narrow end becomes drawn out to form the axis cylinder which continues to increase in length until it ultimately attains its adult proportions. The surface of the cells become rough and spiny and the elongations of these spines produce the dendrites.

The pluricellular theory has been elaborated chiefly by Fragnito. In 1899 and again in 1902 he described the development of the nerve cells in the chick. He believes the germinal cells to be quite distinct from the epithelial cells and not to be formed from them. By the 3rd day the epitlelial cells have been converted into a substance termed neurospongium: this is a fibrillated structure of great tenuity which forms a network and which contains blood and lymph vessels. It has developed so far before neuroblasts appear. These are round or oval bodies possessing a deeply staining dense reticulum and surrounded by a very thin layer of protoplasm. These tend to become arranged into groups, and to migrate peripherally: by the 6th day they are incompletely grouped: by the 7th day there are no isolated elements in the anterior cornua of the cord. Each group or colony is composed of 2 kinds of cells:-

1. Primary neuroblasts - may be more than one; form nucleus of the adult cell.

2. Secondary neuroblasts - are several; they form various constituents of cell protoplasm.

These elements are not the result of cell division: Karyokenesis is only seen when the cells are in the vicinity of the central canal: the secondary neuroblasts loose their contour, fuse together and do not stain with thionin. By the 9th day they have practically assumed adult formation.

In 1905 Capobianco confirms Fragnito's findings with regard to the nerve cell development; he thinks that the movements of the neuroblasts in the earliest stages, when they find their way from the neighbourhood of the neural canal to their ultimate destination to be due to chemiotrophism. He also brings forward very interesting evidence to support the pluricellular origin of nerves. He compares the number of neuroblasts with the number of nerve cells formed. If it can be shown that there are fewer nerve cells than neuroblasts it is very suggestive of the cells being formed by blending of several neuroblasts. He finds that in two casesthe proportion of neuroblasts to nerve cells was as 2·83 to 1· and 3·02 to 1.

A similar mode of development has been advanced for the protoplasmic processes. Fragnito in 1903, at the same time that he described the development of the nerve cells, dealt with that of the processes and peripheral nerves and pointed out that they were formed from rows of cells which unite to form a fibril. These fibrils are beaded: the beads are supposed to be due to a persistence of the cells. The process consists in the development by the cell of 2 processes which unite

with similar processes from other cells on either side and thus a fibril is formed. The nucleus in time disappears. These fibrils become appressed to form the axis cylinder, one end of which is able to become fused with the secondary neuroblasts at the periphery of the cell. The dendrites are similarly formed. Later he thinks he has been able to trace the intracellular course of the fibrils which pass right through the cell.

The phenomena characteristic of the central theory of regeneration follow the wellknown changes which are included under the term Wallerian degeneration which affects the peripheral end of the cut nerve and also part of the central end, and which consist of breaking up of the myelin sheath and axis cylinder into fat droplets which become absorbed and leave the neurolemmia empty. The regeneration process begins at the central end and consists of elongation of the axis cylinder which tends to grow along the neurolemmia sheath when not interfered with by the presence of cicatricial tissue or other cause.
As it grows it becomes invested with a myelin sheath. The process of regeneration is complete in about 2 months. The new fibres supply exactly the structures which the old fibres innervated and are in connection with the same central cells. The neurolemma thus acts as a guide for the young fibres and conducts them to the various tissues they are to supply.
The peripheral theory of generation and regeneration of nerves was advocated by Büngner in 1891 and has

since been supported by Eichhorst, Neuman, Tizzoni, Bethe, Beard, Fleming, Ballance and Purvis Stewart. According to these observers, after section of a nerve degeneration begins in the peripheral end in a few hours, progresses and is complete in 3-4 weeks. The nuclei of the neurolemma sheath take on the function of neuroblasts; become arranged in rows and give rise to axis cylinders and myelin sheaths. Experimentally Bethe claims to have demonstrated the accuracy of the peripheral theory. In a series of experiments he cut the peripheral nerves, prevented the central end from uniting with the distal; allowed union to take place, stimulated the peripheral end with a weak current and got contraction of muscle. Contraction did not follow stimulation of the central end. Münzer is unable to accept Bethe's findings, he thinks anastomosis must have taken place. Fleming believes that peripheral as well as central regeneration takes place. The phenomenon of rapid appearance of sensation (1-2 days) after division of peripheral nerves as observed by Bowlby, McCormac and Kennedy might be explained by anastomosis of the nerve twigs in the vicinity; also by theory of peripheral regeneration.

The question is still in an unsettled state but there is enough evidence to support the autoregeneration of the peripheral nerves to merit serious consideration.

The appearances presented by the intercellular and especially the immediate pericellular structures are extremely difficult to correctly interpret. That

specialized pericellular structures exist must I think be allowed, at any rate in the case of the larger cells of the cerebral cortex and in those of the medulla and cord. In the human subject the colloidal silver method shows differentiated structures in each of those regions. This method shows many of the large pyramidal and ganglion cells to be enveloped in a reticulum, the meshes of which are somewhat different in form from those which are seen in the cell body. They are more rounded , and the fibrils which form the meshes are of finer calibre. The reticulum is intimately associated with the cell body and appears in continuation with it and it envelopes the cell body and is prolonged on to the dendrites and axis cylinder; and is seen as a sort of rudimentary web at the origin of the processes. There is frequently seen a distinct, fairly regular line which marks the boundary of the cell and on the outer side of this line is the covering described. Futher in some of the cells the dendrites are seen passing out from the cell body and carrying with them a sheath exactly in the same way as the spinal nerves passing out from the cord carry on them a covering of the meninges.
In the cat similar coverings are seen in specimens prepared by Ramon-y-Cajal's No.3. method. Here the strands of network are much finer than the other fibrils. The adjacent cell processes are often seen to lie on this net, but not to become fused with it. The exact terminations of these fibres cannot be accurately determined by means of this method because

of the comparative coarseness of the deposit. In preparations by the former method however, very similar appearances are seen and I do not think that it can be maintained that true anastomosis takes place.

In Purkinjes' cells by means of Ramon-y-Cajal's process the basket network is well shown and is seen to form a dense reticulum round the cell bodies and to be prolonged as a much finer structure for some considerable distance along the processes.

I have endeavoured to work out the pericellular structures in the cells of the spinal cord of the ox by means of Ramon-y-Cajal's method but for some unexplained reason the prepared tissues have not stained and are quite useless for showing differentiated structure.

With regard to this very debatable question of pericellular structures and mode of termination of fibres, I agree with those observers who maintain that the pericellular networks are demonstrable structures, and I believe them to be distinct from the endocellular reticulum and that probably it will ultimately be proved that the adjacent fibres end in the meshes of the pericellular reticulum but do not actually become continuous with the nerve cell network proper. I am also inclined to the belief that the pericellular network is different in constitution from the nerve cells and is of the nature of specialized neuroglia. In this connection the findings of Donaggio with regard to what he describes as radiations, are of the greatest importance and point to an ultimate solution of the difficulty.

As yet their exact relationship cannot be held as proved but their further investigation will require to be undertaken.

CONSIDERATIONS ON THE NEURONE THEORY.

The advance of knowledge of the fibrillary structure of the achromatic portion of the nerve cells has stimulated fresh controversy as to whether the nerve cells form one continuous anastomosing structure in which the individual cells are simply minute units which compose a whole; or whether each nerve cell with its accompanying processes is anatomically and physiologically independent and is in relationship with the other nerve cells only by contiguity.

Since what is known as the neuron theory was elaborated by Waldeyer in 1891; and although it has been so generally accepted and used as a basis on which practically all problems of neurology are built up: there have always been a certain proportion of observers who have been unable to reconcile certain clinical facts as well as histological appearances with the theory that each nerve cell is an anatomical and physiological distinct unit. But that the clinical facts and histological pictures can only be explained by supposing that the processes of each nerve cell anastomose with similar processes from other nerve cells to form a vast complicated network in which the various mental acts are elaborated.

The criticisms which have been offered easily fall into 3 periods:-

1. From 1891 to about 1897.
2. From 1897 to about 1900.
3. From 1900 onwards.

During the first period Golgi was the chief critic and his criticisms were based on appearances which brain

sections showed after treatment by his well known method by which he thought he was able to demonstrate a network round the nerve cell and closely applied to it. Thiswas generally regarded as being of the nature of an artificial product of staining.

When the investigations of Bethe and Apathy placed the fibrillar structure of the achromatic portions of the nerve cell on a firm foundation and by their methods alleged to have demonstratedanastomosis between the cell processes; considerable force was given to the arguments against the neuron theory acceptance. Apathy's conclusions with regard to the anastomosis of nerve cell processes in invertebrates and the histological pictures which he was able to shew, left little doubt in the minds of most investigators that he had established his thesis. He was unable however to bring forward proof of a similar anastomosis in the case of vertebrates. Bethe attempted to establish the theory that all nerve functions were performed not within the cell bodies but in the intercellular network. His work was carried on on material obtained from vertebrates and he asserted that he was able to demonstrate a diffuse pericellular network in which neurofibrils anastomosed. Experimentally he endeavoured to support his criticisms by results on carcinas maenas. He separated the fibrilsfrom the ganglion cells supplying the second antenna and was able to excite in the injured part the movements of flexion and extension. Such a result is however very inconclusive as was pointed out by Lenhossek and others, as stimuli could very conceivably be trans-

mitted from sensory to contiguous motor fibres.
In 1898 and 1899 Lugaro lent his weight of authority in supporting the neuron theory and in strongly criticising the conclusions of Bethe and Apathy. He foreshadowed a view that he later on laid more stress upon viz., that the demonstration of mere continuity of nerve fibrils would not necessitate the entire destruction of the neuron theory: that were Bethe able to conclusively prove that acts took place in the intercellular network, and that the nerve cell only exercised a tropic function, it would not seriously interfere with the theory in so far as it affirms an embryological and tropic autonomy.
But Bethe has never observed anastomosis between neurofibrils from different cells, or at any rate he has not been able to demonstrate the connection beyond doubt, nor has he observed free terminations of fibrils.
Lugaro's conclusions are all based on the acceptance of the monocellular origin of the nerve cells. He accepts Apathy's demonstration of fibrillar anastomosis in the case of the invertebrata; but he points out that it is impossible to argue that similar conditions apply to higher animals. He thinks that continuous fibrillar anastomosis represents an arrangement by which much simpler acts are accomplished: that nature has found it more suitable to fuse the "independent embryological neuronic individuality"; whilst in other cases where there is considerably more call on fine nervous interworkings, as in the higher mammals, the independence of the nerve units is preserved as it is more easy to establish associations in complex acts

by simple contiguity. Besides, the existence of a pericellular reticulum implies a certain amount of curtailment of associative processes or of new acquisition of intelligence and is more suitable for reflex acts. Lugaro further accuses the critics of the neuron theory of not taking into consideration the laws of development of nerve cells and their degeneration, and of the orientation of the axis cylinders. But in the light of later knowledge the researches in these departments tend to support the criticisms of the theory. Lugaro points out that Bethe, Apathy and Nissl think that the want of demonstrated continuity is due to imperfections in Golgi's impregnation processes: but he maintains the interruption is not accidental but is actual. Van Gehuchten and Barker also support Lugaro's reasoning. Ford Robertson thinks that Lugaro's view with regard to the occurrence of fibrillar anastomosis in invertebrates and the want of its demonstration in vertebrates, and his interpretation of the appearances are of very great importance and allow the neuron theory to be retained but "altered only in respect of its being qualified by an exception of great scientific interest but of no practical importance".

The 3rd period that has been taken viz., from 1900 onwards, has seen the elaboration of more arguments against the neuron theory. The chief of these is the elaboration of the pluricellular origin of the nerve cells by Fragnito and his followers; and further experimental researches with regard to nerve

regeneration after section. An outline of these investigations has already been given.

1903 saw the publication of strong criticisms against the neuron theory by Kronthal and Bethe, and its support by Münzer. The former takes as proved the theories of Bethe and Apathy and bases his arguments upon them. He maintains that phenomena following stimulation of the cortical grey matter is due to excitation of the fibres of the intercellular plexus; that the nerve fibres neither begin nor end in the cells: that the latter are only points of exchange, that in starvation other body cells use up fat, but brain cells do not, consequently they are not true organisms: that they arise from a coalescence of leucocytes, that they have no real nervous function and that they play a passive rôle and act only as insulators. Kronthal thinks that psychical processes are the properties of the organism as a whole and not of individual cells. The majority of this observer's arguments are thus purely hypothetical and are founded on wholly insufficient evidence. Further experiments already mentioned by Bethe on sectioned peripheral nerves must be regarded, in the light of Münzer's criticisms, as improved. Further, Fleming, as the result of his experiments, thinks there is peripheral regeneration but he also feels sure that central regeneration is present as well.

Durante in 1904 condemns the neuron theory on all points. Embryologically, histologically, pathologically, and physiologically, he considers the theory to be untenable. He maintains as proved the pluricellular

origin of nerve cells and fibres: that each inter-annular segment of the axis cylinder is composed of something of the nature of a nerve cell, consequently in diseased conditions, e.g. neuritis or injury, degeneration is unequal in the course of the process. He also maintains that regeneration of the axis cylinder has occurred after the destruction of its nerve cell and that the disproportion between the bulk of the axis cylinder and the nerve cell is against the former being developed from the latter. With regard to nerve conduction he believes that the fibres are not merely inert conductions but that each segment takes an active part in the conduction of the impulse and that the relative slowness of nerve transmission is due to time occupied between the neuroblasts each of which is active in the process. In a later paper he elaborates his published views and suggests that nerve cells are analagous to the lobules of a glandular organ. "The conception of a nervous system composed of primitive polycellular masses analagous to the lobules of glandular organs is best in agreement with known facts: while each cell of such a lobule (i.e. the constituent neuroblasts) has an individual life, and reacts individually to pathogenic agents, it is also dependent on anything which affects the lobule (neurule) as a whole". He proposes to drop the term neuron which implies an anatomical unit, and substitute neurule to designate functional units, polycellular in origin, and in physiological unity, like a glandular structure. In a paper published in October 1904 Bethe states the

arguments for and against the neuron theory. In brief they are as follows:-

Neuron Theory

For.	Against.
1. Each neuron is a development unit arising from a single embryonic cell.	Regeneration of peripheral nerves is independent of the ganglion cells
2. Each neuron is an anatomical unit comprising dendrites, ganglian cell &c.	The multicellular origin of the peripheral nerves is undoubted.
3. There are no nerves apart from neurons.	It is highly probable that nerve units apart from neurons exist and are genitically independent.
4. The neurones are in contact but not in continuity: the dendrites and nerve terminations end blindly.	Both in invertebrates and in invertebrates there is a true anastomosis between the different nerve cells in the fine nerve network of the grey matter; and fibrils can be traced from one neurone to another.
5. The neuron cell is a trophic unit.	Degenerative changes following various lesions are not restricted to the neurone primarily affected.
6. Physiologically the dendrites are the organs of reception: the axone is the organ of discharge.	

In a paper written by Lugaro and reviewed by Ford Robertson in October 1904 a further attempt is made to present the evidence for and against the continued acceptance of the neuron theory. Lugaro maintains that neither the pluricellular origin of the nerve cells nor the autogenous regeneration of the peripheral nerves, nor the continuity of the neurofibrils as maintained by Bethe nor the presence of Golgi's pericellular network is proved beyond doubt. But were these each and all proved to be correct Lugaro argues that the neuron theory would not be destroyed. He elaborates the views expressed by himself in 1899 & points out that the anatomical unity of the neuron is conceivable in 2 senses:-

1. In a narrower sense as implying a cellular unity.
2. In a wider sense "as an organic individuality", as a complete organ, leaving unprejudiced the question of its embryological origin and of its cellular "unity".

If the previously mentioned arguments were proved; the neuron might still be regarded in its wider sense as an organic individuality.

Has enough evidence then been brought forward against the theory of cell indivuality to justify the Neuron Theory being substituted by one which holds that there is cell to cell continuity? I am of the opinion that, as yet, there has not. Even Bethe, who is the most active opponent of cell indivuality, has not been able to demonstrate indubitably that there is a true anastomosis between the processes of one cell with those of another: and it must be admitted that his method for demonstrating the internal arrangements of the nerve cell, chiefly on the results of which most of his arguments are founded, does not show the true reticular arrangement. It is a curious fact that other tinctorial methods do not show the continuity of the fibrils so unquestionably as Bethe claims for his. It is, I think, scarcely possible to theorize on the results obtained by impregnation with silver nitrate by any of its modifications; and it would be better to still regard it as a useful adjunct to anatomical study. The further elucidation of the relationship of the pericellular nets and the connections of the "Radiations" of Donaggio will probably help to throw further light on the mode of termination of the nerve endings of cell and cell. The pericellular net is closely applied to the cell body but its appearance is such that it might with certainty be regarded as a structure distinct from the cell body by reason of its meshes being of different form and the threads of which it is composed of different character to those

of the cell body proper. It seems to me that the modifications which Lugaro suggests - viz, each cell as an "organic indivuality" can scarcely be permitted if the Neuron Theory is to be maintained. Relationship of cell to cell by contiguity is the main argument for the theory; and if continuity can be proved, it necessarily follows that nervous phenomena must be explained on a different conception of cell arrangement: besides it is not quite clear what Lugaro means by "Organic indivuality" or of how he proposes to correlate it with continuity of fibres, as he must consider that there is strong evidence of continuity or of the pluricellular origin of nerves. The embryological nerve cell investigations of Fragnito, Capobianco and others; and the accumulating evidence of peripheral regeneration of nerve fibres are certainly very suggestive: but on a matter of such moment and one so full of debate, there has been too little confirmation of the findings; and consequently it must be still held that the Neuron Theory is best suited to explain the various nervous acts.

In making this statement I am not oblivious to the accumulating mass of evidence and criticism that has been levelled against it and which includes all the work by the various investigators already mentioned. It would be unwise to set aside the results of Bethe and his co-workers and of the embryological studies of Fragnito and the others; or of those observers engaged in the study of nerve regeneration. In fact at the present time many of the results brought

forward in these fields of research tend to support their views; but the question of the pericellular structures and the mode of termination of the nerve endings are still undecided; and until these vexed questions are indubitably settled it would be unwise to condemn so good a working hypothesis, as the Neuron Theory undoubtedly is.

PATHOLOGICAL CHANGES IN THE NEUROFIBRILLAR ELEMENTS OF THE NERVE CELLS.

Until within the last two or three years very little attention has been paid to the changes which follow experimental lesions on achromatic elements of the cell. Marinesco, Lugaro, Van Gehuchten, had betwen 1896 and 1900 studied the effects produced by various lesions on the chromatic elements of the cell, and incidentally had observed a disintegration of the trophoplasm or achromatic elements; they had distinguished 3 changes in the nerve cell which followed section of the axis cylinder, viz., reactive, degenerative and reparative: characterised in the first place by increase of cell volume and increased density of staining; later, by the appearance of many pale degenerated cells, side by side with very much swollen cells which later diminish in volume: chromatolysis; displacement of the nucleus; powdery appearance of the chromatic elements; loss of striation, and according to Van Gehuchten a reconstruction of the chromatic elements. In 1903 Lugaro distinguished 2 kinds of lesions,

1. Secondary alterations due to indirect traumatism.
2. Primary alterations due to toxic or nutritive causes.

The former which is the more intense lesion, consists of central chromatolysis with displacement of the nucleus to the periphery: the latter of peripheral chromatolysis without displacement of the nucleus. Fleming and Cox had already pointed out that peripheral chromatolysis with central nucleus sometimes occurs after section of posterior roots: and Marinesco shows that after tearing out of the nerve roots,

complete dissolution of the chromatic substance may take place; the nucleus may not be displaced. Atrophy and degeneration may follow.

Marinesco in 1904 endeavoured to trace changes in the fibrillar structure ~~changes~~ of the cells of divided nerves. He used Ramon-y-Cajal's new fibril stain: 10 days after section;- Fibrils, pale reddish coloured, granular: the spaces occupied by Nissl bodies were diminished in size; nucleolus pale.

Marinesco confirms these findings and points out that the changes vary with the severity of the lesion; that they are much more severe after tearing than after simple cutting. After evulsion the nucleus becomes swollen and pale, the fibrils of the cell body are granular and the reticular appearance is lost. To begin with the changes are present in the cell body; later fragmentation of the fibrils in the processes takes place and finally the cells diminish in volume, lose their processes and have a granular and brownish red colour.

After section there is pallor, reddish discoloration, granularity and approximation of the fibrils and more or less complete disappearance of the reticulum, The disappearance of the network after simple section may be due to dissolution of the chromophile substance and approximation of neurofibrils.

After ligature of the abdominal aorta he has observed fragmentation of the neurofibrils within 4½ hours.

After rabies there occur fusiform thickening of neurofibrils in region of cord, bulb and spinal ganglia, and it has been pointed out by Ramon-y-Cajal

that thereis a simplification of the fibrillor network fusiform thickening of the primary fibrils and presence of abundant yellow pigments. Marinesco produced rabies in rabbits with a view to further study of the special nerve cell lesions in rabies. He finds that h there is thickening of the fibrils; the nucleolus appears as if devoid of granules; and that there are reddish yellow colored corpuscles with one or more granules present in their substance. In the spinal ganglion cells there is a loss of fibrillar reticulum in the central part; the cells with concentric fibrils, or the clear cells are affected to a less degree.
The thickening of the fibrils and the nuclear changes, Marinesco thinks are due to the specific poison of rabies. In the cells of the spinal cord of guinea pigs killed by tetanus, the red fibrils are mostly affected; there may be only granular disintegration and fragmentation of the fibrils up to complete degeneration and extreme pallor of the cells: they may be diffuse or peripheral or principally effect the region of the axis cylinder: the nucleolus is pale and the number of granules is diminished.
The post mortem changes include granular disintegration within 24 hours; after this retrograde changes are rapid: the cells with red fibrils are affected more rapidly than those with black.
In general paralysis he has noted thickening and granular disintegrationof the neurofibrils and cortical nerve cells: he thinks that the cells with red neuro-fibrils are more vulnerable than those with black.
Donaggio and Fragnito in 1905 recorded results of

experiments which consisted in noting the effects on the neurofibrils of tearing out the sciatic nerve of rabbits. In the motor cells the endocellular fibrillary reticulum showed the meshes compressed and regular, there was swelling of the cell, increase of staining reaction of the whole cell but faintness of reticulum and fibrils of protoplasmic processes. Later the reticulum becomes more distinctly stained but is altered in its arrangement. It afterwards more nearly approaches the regular arrangement: but the cell gradually atrophies and the reticulum follows suit. In some of the other elements the nucleus did not differentiate, and was strongly stained; the reticulum being less colored. The peripheral long fibres failed to show this altered coloration and appeared thickened as if from fusion.

These authors regard the grave and rapid destructive lesions described by Marinesco to be partly due to the technique he employed.

Marinesco describes a set of changes which result in the repair of neurofibrils after section. His observations were made on the hypoglossal nucleus. 29 days after nerve section the fibres are undergoing either atrophy or repair. He divided the altered cells into 4 groups:-

1. Atrophied cells shewing only the debris of fibrils.
2. Cells with network less well indicated than in normal cells.
3. Cells showing neurofibrils interlacing with occasional network.
4. Cells with striated appearance- fibrils parellel- sometimes interlace.

48 days after section- striation is more marked, neurofibrils hypertrophied: a few cells show reticular structure round the nucleus.
62 days: volume of cells slightly diminished: reticulation marked;
100 days; development of network much more marked: the neurofibrils of protoplasmic processes are increased in size, are directed toward the cell centre and are lost in the perinuclear network.
The generated network differs from the original in that the strands are less regular and fine, thicker and more opaque and hypertrophied.
In the majority of spinal ganglion cells and in the hypoglossal, the modification of the neurofibrils in reaction and repair begins around the nucleus.

Various changes have been described in the modification of arrangements which the fibrillar elements undergo in various diseased states. These changes and the condition in which they have been noted are described by Marinesco in Myelitis: Meningitis; and Softenings of the Brain. When the neurofibrils are acted upon by toxins or by physical agents they exhibit pallor, granularity, disintegration, fragmentation, partial or complete degeneration or a widely spread thickening. These may commence at various parts of the cell- either at centre or periphery, or diffusely. They are accompanied by chromatolysis, the two progressing pari passu. Vacuoles are sometimes seen and are due to destruction

of fibrils: the nucleus is often displaced to one or other part of the cell and it has been found that the fibrils are affected most in the regions of the cell which are furthest from the nucleus: the area of atrophy is greatest when the nucleus is displaced to the periphery.

In multiple sclerosis Dr Strähuber believes that fibres are generated and undergo myelination, but Max Bielschowsky hesitates in concurring in this view although he does not deny it.

Ramon-y-Cajal and Dalmatio Garcia give a detailed account of the lesions produced in the nerve cells by the virus of rabies. They divide the changes into three classes:-

1. Phase of paresis - begins 7- 8 days after innoculation.
2. Phase of hemiplegia- coincident with the 8th day.
3. Phase of total paralysis- immediately preceeding death; about the close of the 9th day.

In the first instance there is partial and fusiform hypertrophy of the fibrils as if a number had fused together; later vacuolation of the cells is seen. The stage of hypertrophy is followed by atrophy which is characterized by the enormous resistance of the neurofibrils to stimulation; they hypertrophy, form dense fasiculi, include phagocytes which create vacuoles: the fibrils may even extend outside and the axis cylinder may persist even when the nerve cell is atrophied.

They believe that the hypertrophy is produced by the reaction of the neurofibrillary apparatus to stimulation

and that this is expressed by atrophy of the secondary fibrils; the coloring matter of which becomes concentrated in the primary fibrils: this causes increase in their size and the formation of large spaces filled by cellular fluid. This hypertrophy coincides with functional disturbance, it is produced in some animals by cold or by heat and in young nerve corpuscles exposed to cold.

The state of paresis corresponds to the stage of hypertrophy whilst in the paralytic stage there is atrophy and destruction of the reticulum. The observers think the appearances of the nerve cells are characteristic of rabies.

PERSONAL INVESTIGATIONS.

I have made examination of over 30 cases taken from the post mortem room, in order to ascertain what changes the fibrillar structure of the nerve cells undergoes in the various forms of mental disease. The specimens were taken from each case as it came in: the mental condition of the patient was not ascertained until the microscopical examination was completed. Many of the observations were made by means of Bethe's method: a good number were also studied by the aid of Lugaro's silver process. The methods of Donaggio, Apathy, and Ramon-y-Cajal were at times, also employed.

The parts of the brain examined were removed from the precentral gyrus in every case; in many also, parts of the medulla, cord and cerebellum were examined.

I shall give a general description of the microscopical findings in each group of cases and then a detailed description of the naked eye morbid anatomy and microscopical appearances of a case typical of each group.

Group 1.

General Paralysis,- 6 cases.

There is always seen the well known subpial felting, so frequently present in this disease. The cells of the several layers show great variations from the appearances presented in health. In the small pyramidal layer the cells are always much reduced in number and in staining reaction: in the cell spaces are often seen only slight traces of cell structure: more often however they contain amorphous masses in

which no definite arrangement can be seen. The processes are almost all absent.

In the layer of large pyramidal cells, the cells are more distinctly seen; but few are stained; the fibrillation is faint and much pigment is seen in the cell bodies and lies chiefly toward the base of the cell. Here also a great many of the cell spaces are occupied by little heaps of amorphous material.

In the ganglion layer, the cells are usually clearly shown and they present all stages of change. Their appearance is much altered, their processes are broken off; the cell may be swollen and globose, or shrunken; the perinuclear nets may be seen as a ragged covering: coloration of the individual cells is unequal: the cell body is faintly marked; the apical process well defined and fibrillation distinct; or one part of the cell may be more deeply stained and less affected than another. The endocellular reticulum for the most part is greatly altered; the various condensations are absent, the meshes are larger, their outline finer than in the healthy cell. The presence of pigment is a marked feature; it occupies various parts of the cell; it is most frequently situated at the origin of the axis cylinder, or at one side, or at the insertion of the apical process, or it may occupy the whole cell. It is light yellow colored. In these cases the nucleus is pushed to one or other part of the cell by the pigment mass: the cell reticulum is broken up and pressed between the nucleus and the periphery of the cell. The pigment is contained in a broken meshwork of large spaces and of coarser

fibrils which are different in appearance from those usual to the cell. This network forms spaces also which are irregularly rounded and differ much from those peculiar to the healthy cell.

Case 1. Female aet .admitted 17th April 1903, died 24th Oct. 1905.

Post mortem appearances:-

Skull thick and dense; dura mater adherent to pia-arachnoid and thickened- pia-arachnoid thickened, adherent to cortex, general milkiness of the surface pronounced- blood vessels healthy- convolutions showed no marked asymmetry- consistence uniform and fairly good, grey matter reduced in thickness, striation indistinct- ventricles dilated, contained excess of cerebro spinal fluid; 4th ventricle showed numerous granulations on the floor. Liver very fatty- lungs healthy- heart muscle showed fatty change- kidneys in a state of granular nephritis.

Microscopically- cerebral cortex- Precentral gyrus.

Ground substance- homogeneous, uniformly colored, non-granular. Subpial felting- much increased in thickness, cells few, small, round.

Plexiform layer- cells almost all destroyed.

Small pyramidal cells- cells scanty, faintly colored, granular, fibrillar structure indistinct; processes much broken.

Large pyramidal layer- cells broken up, granular, indicated by small heaps of powdery material.

Ganglion cell layer- cells unequally stained, some show the fibrils in the apical process; in the cell body

the network is well seen but the meshes are indefinitely arranged, cell condensations are absent- pigment large in amount: meshes much larger than those common to the cell, and are frequently ruptured; the nuclei are eccentric- the pericellular network is imperfect and ragged. **Figs. 7, 8, 9, 10, 11, and 13.**

GROUP 2.

Organic Dementia in which Cerebral Softening Has occurred.

The general character of the changes resemble those met with in the former disease but the intensity of cell disintegration is more marked: this might be expected from the greater severity of the naked eye changes, and the more marked vascular disease in the form of peri-an endarteritis. The naked eye appearances of the brain showed it to be of much softer consistence, the superficial layers of the grey matter to be sodden and soft over the general surface. Such prominent gross changes are attended by corresponding microscopical lesions. The ground work or intercellular substance is often seen to be granular, altered in its staining capacity, and the fibre processes of the cells coursing in it, to be broken up. In one or two of the cases examined the superficial softening was so marked as to cause the appearance of spaces varying in size, smooth walled and empty, in the superficial layers of the grey matter, and a destruction of the cells of these layers. Generally a well marked subpial felting was noted; the cellular elements of which were scanty, although a slight round cell infiltration was noted in one or two cases.

The cells of the small pyramidal cell layer were in all cases practically destroyed and encroached upon by the peripheral neuroglial hypertrophy. Remains of the cytoplasm were occasionally seen in the cell spaces and presented a granular, pigmented and fragmented appearance. In the large pyramidal cell layer practically similar appearances were seen; between the individual cells the faint outline of numerous neuroglial cells was noted. The axis cylinders as they streamed through the white substance were noted, especially in one case, to be markedly varicose, thickened and irregular in size. The nucleoli of the ganglion cell layer appeared deeply stained in contrast to the faintly stained cytoplasm and nuclei: the cell bodies showed occasionally slight increase of the pigment; but in the majority of the cases this accumulation was so marked as to fill nearly the whole cell. The pericellular network was sometimes seen in these cells to be applied as a loose covering over the cell but usually it was invisible. In the cerebellum Purkinje's cells were faintly colored; the baskets and prolongations were in distinctly marked. In the medulla and cord the disintegration of the cell plasm appeared to be more advanced than in the cerebral cortex. There appeared to be no healthy cells left in the specimens examined. Pigmentation, nuclear displacement or its total absence, destruction of the cell processes and of the endocellular reticulum were usually so marked as to occasion surprise that the bodily functions could be carried on. Certainly in the cases which showed the changes in their most advanced form the patients were bedridden

and helpless for some considerable time before death. In one case there was a small area of softening in the neighbourhood of one of the medullary nerve nuclei. The cells in the vicinity showed no true cell structure, they were completely filled with pigment contained in large meshes. A few cells were filled with a bright yellow pigment which was not contained in any stained reticulum. The axis cylinders were thickened and uneven- numerous corpora amylacea were scattered throughout the sections.

Case 2. Male aet 60. admitted May 1st 1905, died Nov. 13th 1905.

The patient was admitted in a condition of maniacal excitement from the effects of chronic alcoholism. He had suffered from syphilis many years previously. The excitement continued for two or three months, gradually subsided, then gave place to great mental and bodily enfeeblement, loss of memory, deficient articulation, development of slight apoplectiform seizures, increasing flaccidity of facial expression, inability to use the limbs until he became quite bedridden. A gradual and progressive mental and physical deterioration continued until the patient could not feed himself, could not speak and passed into a sort of semicomotose condition in which he lingered for sometime: toward the end the organic reflexes failed, the skin became atrophic; apoplectiform seizures recurred more frequently until his death.

Post mortem examination- 25 hours after death.

Skull Bones irregularly thickened- dura healthy- pia-arachnoid nonadherent, meshes oedematous, the

fluid was bloodstained- brain convolutions atrophied, pale colored and sodden- striation well seen- the ventricular cavities were not appreciably dilated, the 4th ventricle did not contain granulations- the liver showed marked momolabular cirrhosis- the lungs were in a state of hypostatic congestion- the heart muscle showed marked fatty degeneration- the aortic and mitral valves and the coronary arteries were extensively atheromatous- the kidneys and spleen showed well marked chronic venous congestion.

Microscopical examination.- Cerebral cortex.

Subpial felting much increased- slight small cell infiltration present both here and in the plexiform layer.

Small pyradmidal layer- cells faint, granular, fibrillation much broken, pigmentation much marked: only the outline of many cells present; small round cell infiltration present. Large pyramidal layer- cell plasm faintly stained, often uncolored round the nuclei which were deeply colored.

Ganglion cell layer- diffuse fibrillation of the cells; nuclei faintly stained ; nucleoli deeply colored: the cell body often represented by a mass of pigment which was frequently seen at the origin of the axis cylinder or round the periphery of the cell; pericellular net faint, loosely applied to the cell- fibres irregular in size.

Cerebellum:- Purkinje's cells- bodies faintly colored, the basket networks and processes not stained- the cells of the granular layer were very faint and appeared diminished in numbers with a corresponding increase

of the intercellular substance.

Spinal cord:- The cornual cells frequently rounded, deficient in processes, extremely pigmented, the pigment often filling the whole cell- fibrillor structure granular, undifferentiated; nuclei deeply stained; the cytoplasm much fainter; the axis cylinders thickened and uneven- numerous corpora amylacea present throughout the sections.

Blood vessels showed extensive and widespread peri-and endarteritis so that the lumina of many were quite closed up and of others very greatly diminished in calibre.

Figs. 12, 14, and 15.

GROUP 3.

Dementia associated with various physical disorders- Chronic Interstitial Nephritis, Tuberculosis of the Kidneys & Lungs.

This group includes a series of 3 cases which presented the above mentioned pathological conditions.

There was the usual well marked band of subpial felting in which numerous cell elements were noted. The intracellular structure of the small pyramidal cells was always distinct, broken up and only seen as fragments in the cell spaces: in the processes the fibrillation tended to persist, the greater number of the cells had completely disappeared. In the large pyramidal cells however, the fibrillation was very much more distinct in every case but unequally stained: the cells of this layer vary considerably in size, their nuclei are usually displaced: the cell reticulum

can be seen passing into the axis cylinder processes. Pigment is very large in amount but does not so frequently fill the whole cell. Sometimes the pericellular reticulum is seen distinctly. The ground work throughout the different layers is homogeneous and not markedly granular. In the cells of the ganglion layer there is considerable variations of size and staining. The pericellular reticulum is frequently well seen as a loose meshwork covering the cell bodies and part of the processes. The endocellular fibrillary structure is well preserved, the fibrils which compose it are thickened, and the interfibrillar spaces are large; frequently the perinuclear condensation is well shown. Pigmentation is prominent and affects chiefly the intermediate zone of condensation at the axis cylinder origin: less frequently it is seen at the cell periphery.

Case 3, Female aet 59 - Dementia, old pulmonary tuberculosis; chronic interstitial nephritis, admitted Mch.9th 1905 died, Jan. 14th 1906. The post mortem was made 26hours after death.

The pia-arachnoid much thickened; milkiness slight, adherent in places to the brain cortex- the blood vessels were slightly atheromatous- brain convolutions considerably wasted and atrophic, consistence good and uniform ; grey matter reduced in thickness, darkened in color; white substance also reduced- liver very fatty- lungs showed areas of old tuberculosis- heart muscle soft; friable; aortic cusps thickened and atheromatous- both kidneys in an advanced stage of interstitial nephritis- spleen soft

and friable.

Microscopical Examination:- Cerebral Cortex.
Subpial felting very marked, neuroglia elements numerous. Small pyramidal layer- cells scanty, cell spaces empty, the outline only of the cell is sometimes seen. Large pyramidal layer- cells more numerous, but are irregularly sized, intracellular networks fairly distinct, inequality of staining is very marked- nuclei nearly all stained.
Ganglion cell layer- cells vary in size and staining; the fibrils are thickened; the interfibrillar spaces are large. Some of the cells show appearances as if surrounded by a loosely applied reticular covering, the meshes of which are larger than those of the endocellular reticulum and the fibrils are finer. Extensive pigmentation at the axis cylinder cone and commencement of the process is present; the perinuclear ring is well seen.

GROUP 4.

The next series of 6 cases all present a marked degree of Chronic Brain Atrophy associated with various mental and bodily symptoms. A table showing the various conditions is appended.

1. Female, aet 56.- Melancholia- Chronic brain atrophy.
2. Female, aet 64.- Chronic melancholia- Chronic Brain atrophy.
3. Male, aet 82.-Senile Mania- Chronic brain atrophy.
4. Male, aet 69.-Senile Dementia-Chronic gastric ulcer.
5. Female, aet 65.-Senile Dementia- Chronic brain atrophy.
6. Female, aet - Senile Dementia- Meningeal haemorrhage.

There is a varying degree of thickening of the subpial felting: in some of the cases it is but slightly present; in others it is well marked, the cellular elements being scanty in all cases. The general ground substance varies somewhat in the different cases; it is sometimes deeply stained; sometimes faintly and in one case it is brittle. The small pyramidal cells are atrophied, few in number, stunted, shrunken, and show very few processes: pigmentation is not a prominent feature; fragmentation of the cell network is always present. The cell spaces may be entirely empty or contain little powdery heaps. The large pyramidal cells are also much disorganized and show varying degrees of inequality of staining, fragmentation of the endocellular network, indistinctness of arrangement and granularity: pigmentation is usually present and the nucleus is usually displaced. The ganglion cells are profoundly altered; the chief feature which they present is the presence of abundant deposits of pigment which in many of the cells occupies the whole of the cell space; it is contained in a network, the meshes of which are large and of rounded contour; it is sometimes of a greenish tint but is usually of a very pale yellow color. The pericellular net is frequently seen but it is faintly stained. The cell processes are very much broken up in all the cases. In the cerebellum Purkinje's cells are indistinct, the basket fibrils are colored irregularly and indistinctly, the cytoplasm is frequently homogeneous but sometimes shows fibrillar network.

Case 4. Female aet 65, Senile Dementia; Chronic Brain Atrophy. Admitted 7th July 1904. Died 18th October 1905.

Post mortem examination held 24 hours after death. Skull bones not altered- dura adherent over the vertex to the bones; thich and dense. Pia-arachnoid non-adherent, meshes oedematous; milkiness general - blood vessels are extensively atheromatous - convolutions of brain are much wasted; sulci gape widely; grey matter reduced in thickness; ventricles dilated and filled with C. S. fluid - gall bladder distended with thick, viscid, black colored bile,- liver shaws no naked eye lesion - both lungs very adherent to the chest wall; there is a slight congestion at base of right lung - coronary arteries calcareous- kidneys small and contracted.

Microscopically - Cerebral Cortex.

Subpial felting, slight- plexiform layer, cells scanty- Small pyramidal layer,-cells almost free of pigment; arrangement of fibrils indefinite; fragmentary network in cell bodies.

Large pyramidal layer - fibrillation pale, large amount of pigment present in the cells; outline of many of the cells only shown.

Ganglion cell layer - contain very large amount of pigment which has a greenish tint, occupies cone of axis cylinder or base of apical process and encroaches on the other parts of the cell; the fibrillae pass into it and appear to be broken up; pigmentary meshwork shows larger meshes which are frequently ruptured.

Fig. 17.

Cerebellum - Purkinje's cellsare indistinct; basket network colored irregularly and indistinctly; cytoplasm frequently homogeneous but sometimes shows traces of fibrillar network.

GROUP 5.

Includes 2 cases the subjects of Epileptic Dementia. They both show a remarkable similarity in their microscopical appearance. The usual peripheral condensation of neuroglia is seen. In the small and large pyramidal layers there is a noteable absence of any trace of normal cellular structures: the cell spaces are empty or show deeply stained nuclei or amorphous remains of cells. There is no trace of fibrillar reticulum. In these layers the cells appear to be more profoundly altered than in any of the cases yet examined. In the ganglion cell layer the cells are in various stages of disintegration; they are unevenly stained, parts of the cell body are colored, other parts unstained; pigment accumulation is prominent and usually occupies the intermediate cell zone; the reticulum is usually seen round the nucleus and at the cell periphery. There is only a small proportion of the cells which have retained the stain. In the medulla the nuclear cells are merely outlined and do not show definite structure-
In the cerebellum, Purkinje's cells are pale, the nuclei are deeply colored, the cell plasm is only faintly reticular. The cells of the granule layer are faint and indistinct, appear to be numerically less,

and the intercellular structure to be increased. The molecular layer shows a marked decrease of cellular elements.

Case 5. Male aet 47, admitted Oct. 22nd 1889, suffering from epilepsy, died Feb. 10th 1906 of pneumonia.

Post mortem examination held 36 hours after death. The positive naked eye appearances of disease are only mentioned. The pia-arachnoid thickened and milky; the meshes are oedematous; non-adherent - the brain convolutions are atrophied - the grey matter appears thickened and striation is indistinct - the left lung shows a patch of gangrene at the posterior lobe.

Microscopical examination:-

Cerebral cortex - All the cells of the small and large pyramidal layers are irregularly colored and very few in number; the nuclei are prominent - the cell plasm is uncolored; almost all the cell spaces are empty or only contain small masses of debris.

Medulla - Outline of the cells is only seen - internal structure is in an advanced stage of disorganization.

Cerebellum - Purkinge's cells are pale, nuclei deeply colored; reticulum of cell body very faint - cells of the granule layer are feebly outlined, fibrillation scanty: the molecular layer is almost devoid of cellular elements.

Throughout the brain the vessels show extensive peri- and endarteritis; most of the smaller ones are occluded.

GROUP 6.

Includes one case of diabetes mellitus with an associated mental condition of acute melancholia. The appearances to be described were very striking and created the impression that the staining method was at fault. The tissues were prepared by the colloidal silver process and the sections from the cerebral cortex and medulla did not show one single stained cell: the intercellular substance was beautifully stained; the cortical radiations clearly and sharply defined so that the line of Ballaiger could be determined by the naked eye as a light blue band. The medullated fibres of the medulla were also very sharply defined so that the specimens resembled successful preparations by the Weigert-Pal method. Purkinje's cells in the cerebellum were fairly well demonstrated and that fact served to show that the staining process was not at fault as all the tissues had been prepared together. To confirm this a fresh sample of collargol was obtained and control sections were used. The same result followed in the case of the cerebral and medullary cells viz., an utter want of cell coloration in any of the layers. This is a fact of great interest but one which I have been unable, as yet, to confirm from the work of others.

Case 6. Male aet 62, admitted 6th Jan.1906 suffering from acute melancholia and diabetes mellitus; died 26th Jan. 1906, of diabetic coma.

The patient was a coalminer and a labourer at a forge; he had been off work for over 12 months; he

had been a fairly steady man and a hard worker. The symptoms of diabetes were not diagnosed until he fainted at his work, was removed home and placed under medical care. He was very poor and had an invalid wife; consequently he was unable to obtain proper treatment. He was never again able to follow his employment and sometime before admission he developed mental symptoms of melancholia and showed grandiose delusions, fancying he could cure all kinds of diseases, except diabetes, in a day or two by obviously absurd remedies. He was admitted in a very weak state; was much emaciated: the urine contained a large amount of sugar, acetone and diacetic acid. About a week before death he became very sleepy, quiet, and lost his appetite: the condition became worse, he passed into a semicomatose state until his death.

Post mortem examination held 44 hours after death. Body much emaciated - superficial fat almost absent - cut muscles dark colored - pia-arachnoid increased in thickness, tough and milky in appearance throughout its extent; meshes oedematous - blood vessels not atheromatous but their walls were stiffened and their cut lumina gaped widely - brain convolutions well formed; slight atrophy present - grey matter not reduced, striation well marked - vessels of the centrum ovale show very prominently - ventricles not dilated - other parts showed no obvious signs of disease - mesenteric glands enlarged - mesentery thickened and intimately adherent to the pancreas which was much reduced in size, tough and fibrous and on microscopical examina-

tion showed extensive interstitial pancreatitis - liver very dark colored - lungs oedematous - heart muscle undergoing fatty degeneration; valves competent, kidneys large capsules strip readily; each showed a number of soft white areas on the surface, afterwards found to be loosely formed connective tissue - walls of urinary bladder hypertrophied- the organ contained a quantity of urine which showed a large quantity of sugar, acetone and diacetic acid. The blood, post mortem, was tested for the last two mentioned substances but without success. The bones were increased in brittleness.

Microscopical examination:-

Cerebral cortex - Nowhere throughout the different layers is a single cell stained; the cell bodies appear as uncolored remnants; many of the cell spaces are empty, others contain the outline of cells or little heaps of cell remains. The intercellular substance is remarkably well colored so that the cortical radiations are seen as far as the small pyramidal layer. In the medulla the cells are also devoid of coloration in the nuclei in the floor of the 4th ventricle and in the cells of the olivary nucleus. The medullated fibres are very prominently colored and show well marked differentiation. Fig. 19.

Cerebellum - Purkinje's cells show distinct reticulo fibrillation but there is a marked stunting of the processes. The cells of the granule layer are very pale and indistinct: the molecular layer shows very few cell elements.

GROUP 7.

Chronic Mania associated with Tuberculosis and Fatty Heart.

In this group are included three cases in which the mental symptoms warranted the diagnosis of chronic mania. In two of the cases the presence of pulmonary tuberculosis was found post mortem and in the other case the heart muscle was in a state of advanced fatty degeneration. In general the microscopical findings are not essentially different from those already described. There is the usual want of numerical proportion of cells stained in the superficial layers: the presence of many shrunken cells, the prominence of the pericellular spaces and the deep staining of the nuclei. But it is noted that in both the small and the large pyramidal layers the percentage of cells which show definite structure is much larger than in many of the other groups. Although there is much inequality of staining of different parts of the cell, the impression is obtained that the stage of disintegration is not so far advanced here as in some of the other cases: the pericellular sacs are not seen. The ganglion cells of the cortex show the usual changes of eccentricity of the nucleus, rupture of the internal reticulum and the presence of excessive pigmentation. But at the time of the histological examination, before the mental condition of the patients or any particulars were known, a note was made [redacted] to the effect that the more advanced changes were absent in one case belonging to this group. In the cells of the cerebellum

faintness of staining, increase of the intercellular substance of the granule layer and a want of pericellular fibrils round Purkinje's cells were noted in one of the cases.

Case 7. Male aet. 51. admitted 10th Aug. 1904.
died 21st Jan. 1906.

Chronic Mania. Fatty Heart.

Post mortem examination held 25 hours after death. Body emaciated-, skull bones thinned but not lessened in density - dura adherent to skull and pia-arachnoid which was thickened - blood vessels not obviously diseased - brain large and of good consistence, frontal lobes appeared to be sligltly atrophied - grey matter appeared to be healthy - ventricles not dilated - old perihepatic adhesions which affected the stomach present - liver small, cirrhotic and pale - pancreas increased in density and cirrhotic- both lungs emphysematous - heart muscle friable and fatty - kidneys granular - spleen small and pale.

Microscopical - Cerebral Cortex.

Subpial felting thick.

Small pyramidal layer - cells small, shrunken, cell spaces prominent, frequently contained only deeply colored nuclei or remains of cytoplasm: fribrillation fragmentary and confined to apical process; but many of the cells are more distinctly stained.

Large pyramidal cells - more numerous and more prominently stained than usual, but staining is unequal, parts of the cells are uncolored, especially round the nucleus and origin of the axis cylinder where the

fibrils are fragmentary; sometimes the change extends into the axis cylinder.

Ganglion cells - show all stages of change but not so advanced as in some cases - pigmentation, eccentricity of the endocellular network are prominent features.

Cerebellum - cells pale - reticular structure not well seen, nuclei deeply colored: cytoplasm indistinct; basket fibres are not well colored.

GROUP 8.

Idiocy.

I have only had an opportunity of examining one case of congenital arrest of brain development and unfortunately the results obtained are useless from a histological point of view on account of the great softness and advanced stage of disintegration of the brain substance at the time of the post mortem. The disintegration in this case was aided by the ridiculous and ruinous habit sometimes in vogue of stripping the pia-arachnoid from the whole brain surface when the parts are required for microscopical study. The case was that of a boy, aged 11, who died on Mar. 16th 1906. The post mortem was held 31 hours after death. The dura was thickened and adherent, the pia-arachnoid oedematous and milky along the lines of the larger vessels- there was no appreciable atrophy or asymmetry of the brain convolutions but the sulci were noted to be more shallow and microgyria to be present.

The consistence was much reduced, the cortex sodden, and the basal ganglia also sodden and soft. There

was extensive tuberculous infection of the intestinal tract and of the lungs, and lardaceous degeneration of the liver, spleen, kidneys, and other solid organs. Microscopically.- The grey matter of the cortex was completely broken up, so that only fragments of cells remained - these appeared scanty and pale. In the cerebellum the same disintegration was present so that a description of the findings would be of no practical importance.

As a result of these observations it is seen that the achromatic structure of the cells undergoes very profound alterations in the various diseased mental states, and that the changes in these various states bear a close resemblance to one another and also to those recorded by other observers as the result of experimental investigation. But whilst the general nature of the changes, as might be expected, is the same throughout, the intensity varies in the different groups of cases. In dementia associated with cerebral softening the pathological alterations have reached their height; the superficial cell layers are practically all destroyed and the cells of the ganglion layer are affected to a greater degree than in other conditions. The extracellular fibres also show the diseased conditions of varicosity and variation in size. Chronic brain atrophy also exhibits appearances which must have a profound affect on the functional activity of the units concerned. The case of melancholia associated with diabettes mellitus is very striking and remarkable for the total absence of

stained cells, but the fact of its being a single case and so unconfirmed scarcely gives it the significance that similar changes found in other cases of diabettes mellitus would confer upon it. In the meantime therefore it can only be regarded as an interesting condition. The presence of pigmentation in the cells is an almost universal condition; the amount is often so large as to totally fill the cell to the exclusion of other structures. It is of the pale yellow variety except in some conditions of dementia with cerebral softening when it was noted to be bright yellow colored. The question of the origin of nerve cell pigment which is so frequently met with in diseased conditions is still unsettled. It is very frequently found at the part of the cell at which there is supposed to be greatest functional activity, but this part may be quite free of it and accumulations occupy the base of the apical process or the peripheral parts of the cell. It appears as if it might result from the breaking down of some element of the cell and that the metabolism had not advanced sufficiently to allow of its absorption: that is to say it is a product of partial breaking down of cell structure. It is usually contained in a reticulum the meshes of which are large, irregularly rounded or angled, and the fibrils which form the meshwork thicker than those of the physiological cell reticulum. Marinesco thinks that the pigmentary reticulum is distinct from that of the cell and its general appearance tends to confirm that view. That it tends to undergo a physiological

increase in old age is a well known fact but that it is also unusually increased whenever almost any profound change affects the cells is also established on sure foundation, especially if the lesion is of a chronic nature and associated with disease of the vessels. This implies a gradual interference with the normal nutritional supply to the tissues; and it is easily conceivable that such a reduction of nutrition would result in diminished metabolism within the cells and so to an accumulation of partially reduced effete bodies which appear as yellow colored pigment.
The question however is one for still further histo-chemical investigation.

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The principal monographs published in French and German have been read in the original; for those written in Italian I have had to rely on the excellent abstracts chiefly made by Drs Ford Robertson & Orr.
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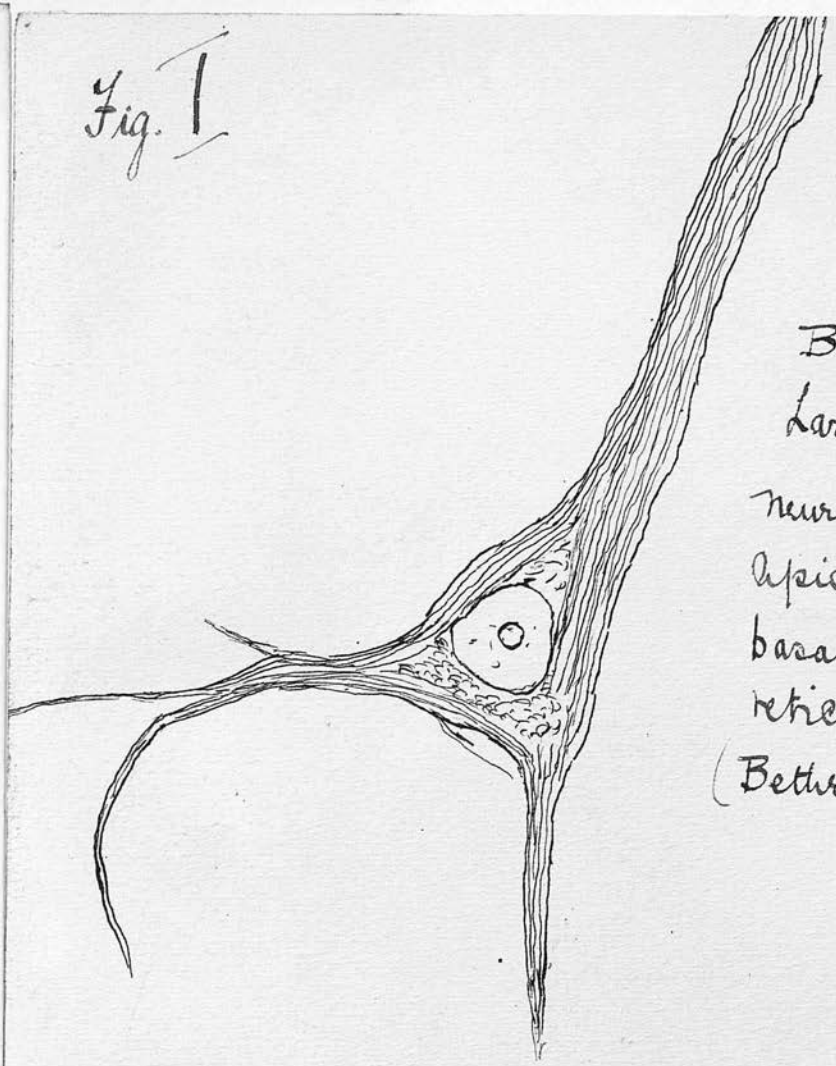
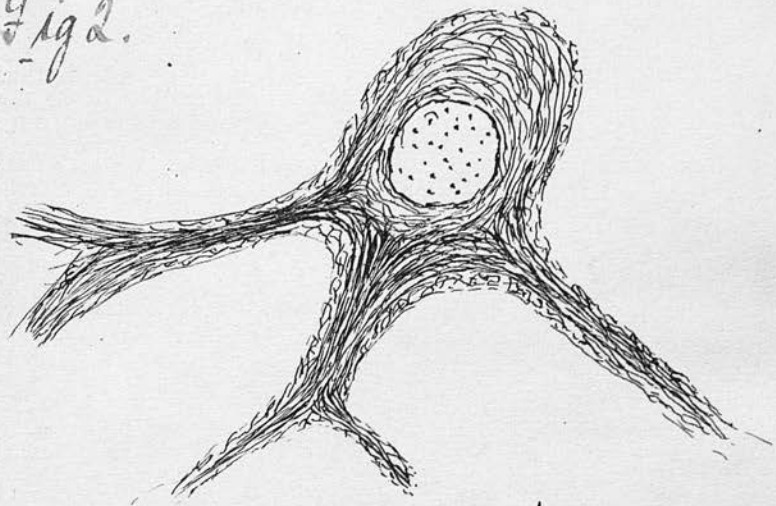
Fig. 1



Brain of Sheep.-
Large pyramidal cell layer.
Neuro-fibrils traced from
apical process into
basal processes: undifferentiated
reticulum at base of cell.
(Bethe's Method - Leitz 1/12th oil Imm.).

Fig 2.



Cell from motor Cortex of Sheep.
Bethe's Method. (CAM. luc. Leitz 1/12 O.I)
Pericellular Reticulum envelopes cell body & processes.

Fig 3.

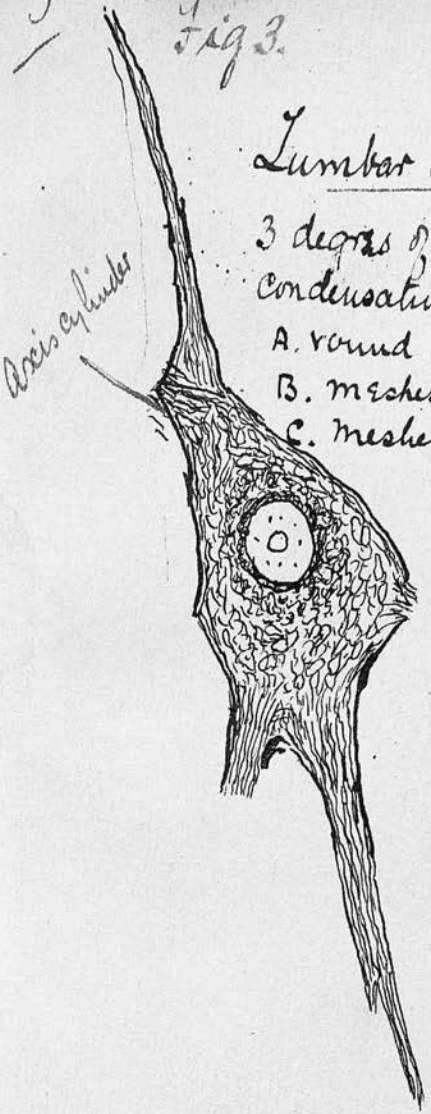
Lumbar Cord of Ox.

3 degrees of intracellular condensation shown.

A. round nucleus

B. meshes slightly larger (middle)

C. meshes much larger (outside)



Medulla of Pig. Fig 4.

Lugaro M. (Leitz 1/6 - 2)

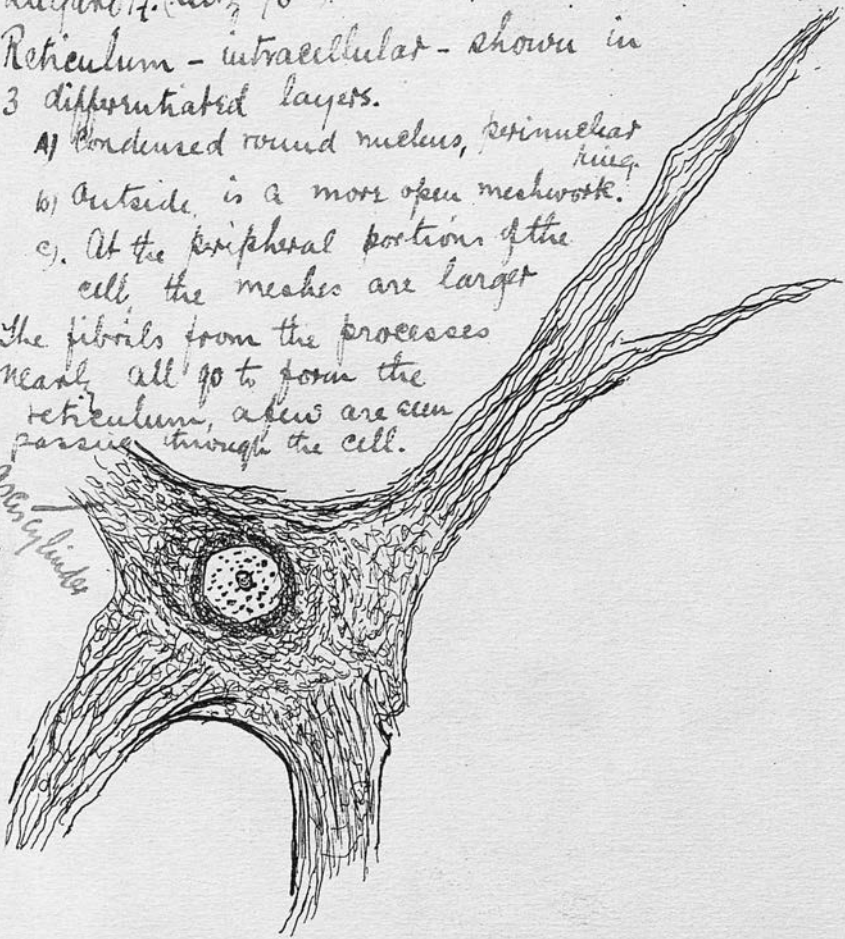
Reticulum - intracellular - shown in 3 differentiated layers.

A) Condensed round nucleus, perinuclear ring.

b) Outside is a more open meshwork.

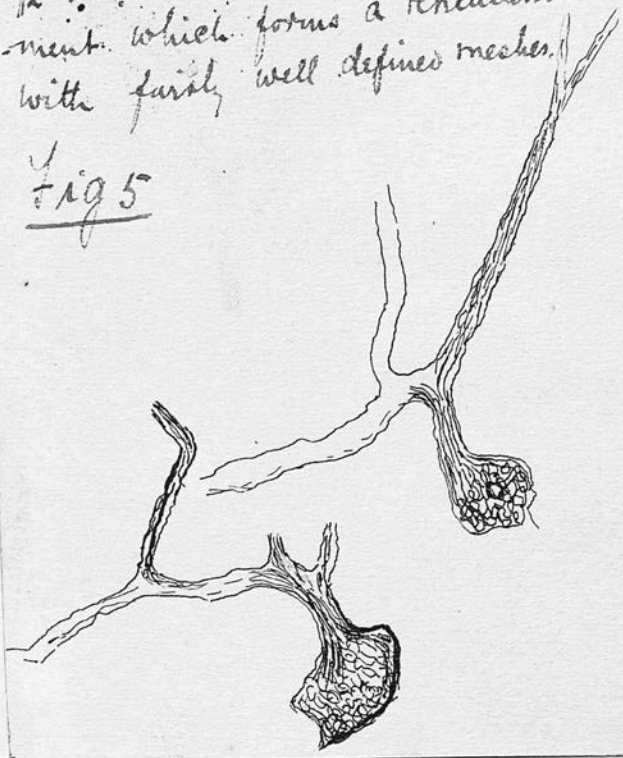
c). At the peripheral portion of the cell the meshes are larger

The fibrils from the processes nearly all go to form the reticulum, a few are seen passing through the cell.



Brain of Pig.
Nugaros Method - Leitz obj. 1/6" -
The fibrils are indistinct in some parts of the processes, but with 1/12 O.I. there is seen an interlacement which forms a reticulum with fairly well defined meshes.

Fig 5



Brain of pig: Bethe's method – Leitz 1/12 O.I.

Ganglion cell.

Fibrils distinct but unequally stained in the apical process; their course is obscured at the base of the cell at the origin of the axis cylinder which seems to be twisted upon itself.

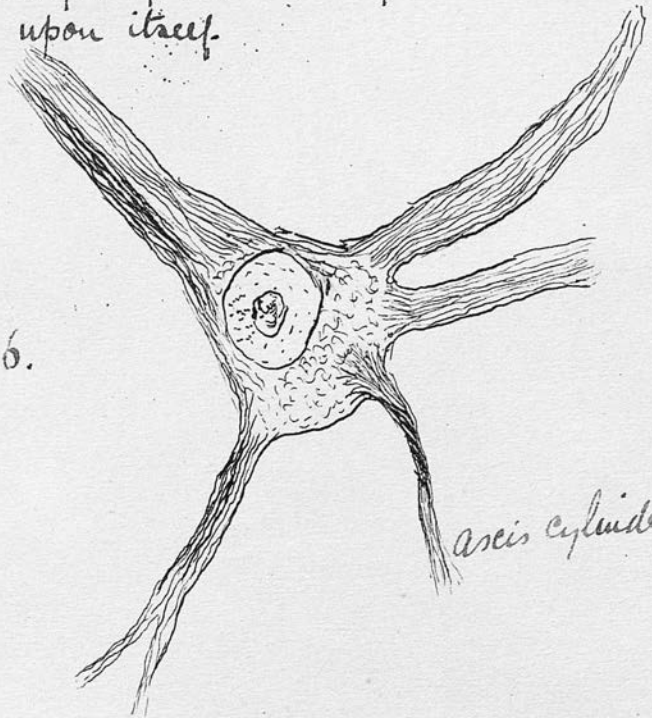
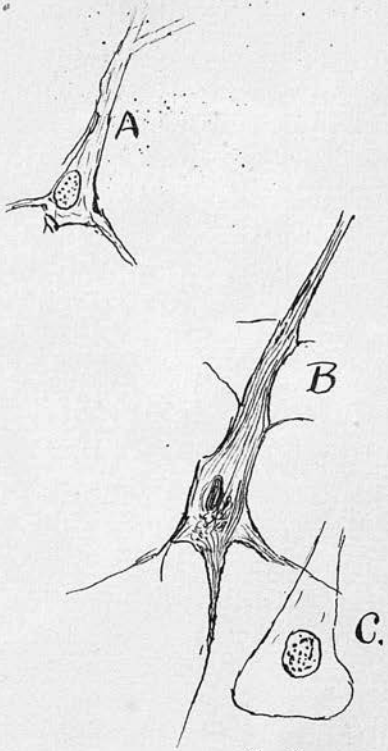


Fig 6.

G.G. Fig 4.



From the pyramidal cell layer.
Cerebral Cortex.

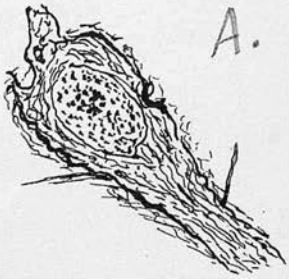
Group of 3 cells -

B. fibrils well shown.

A. " less distinct & broken up

C. " absent.

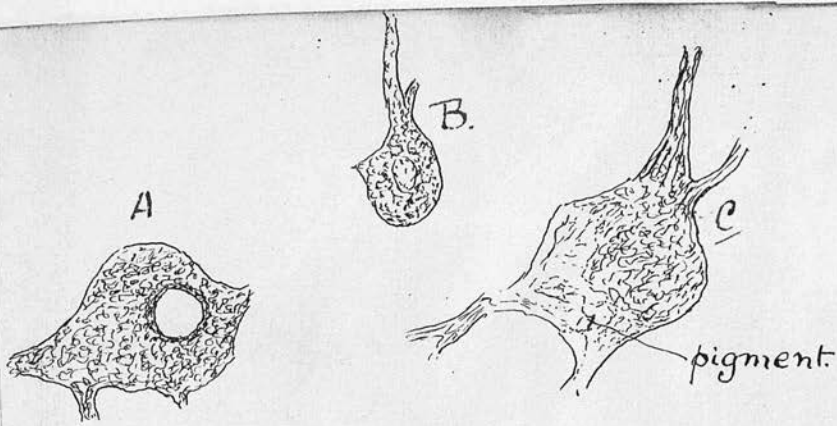
Figs.



A.

B.

G.G.



A. O'N.

Group of cells from ganglionic layer. There is scarcely any trace of fibrils left in the processes: the endocellular reticulum has lost its differentiation except a trace of perinuclear ring A. The processes are stunted, the nucleus of A is eccentric. In C a large portion of the cell is filled with yellow pigment.

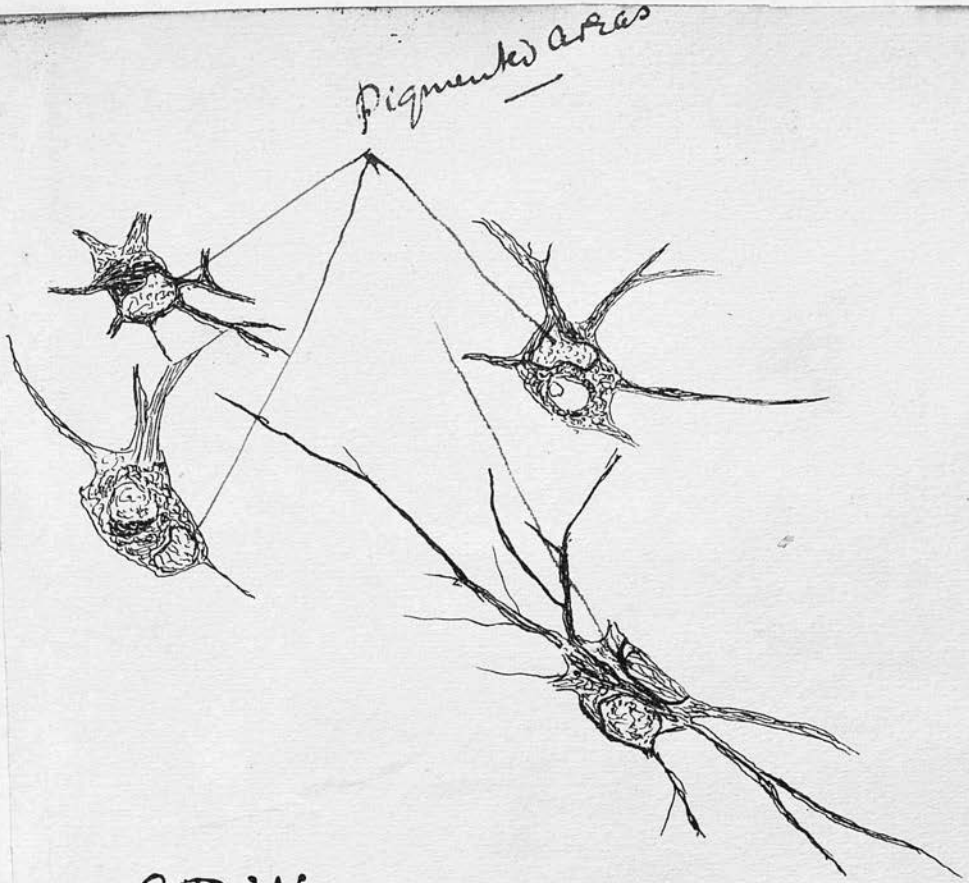
2/3 Fig. 9.

General Paraly

A O'N. 1/4 10.

From same case as former.

Intracellular network not well stained, is homogenous and the meshes broken up. much pigment at the core of the axis cylinder. fibrils of the axis cylinder seen.

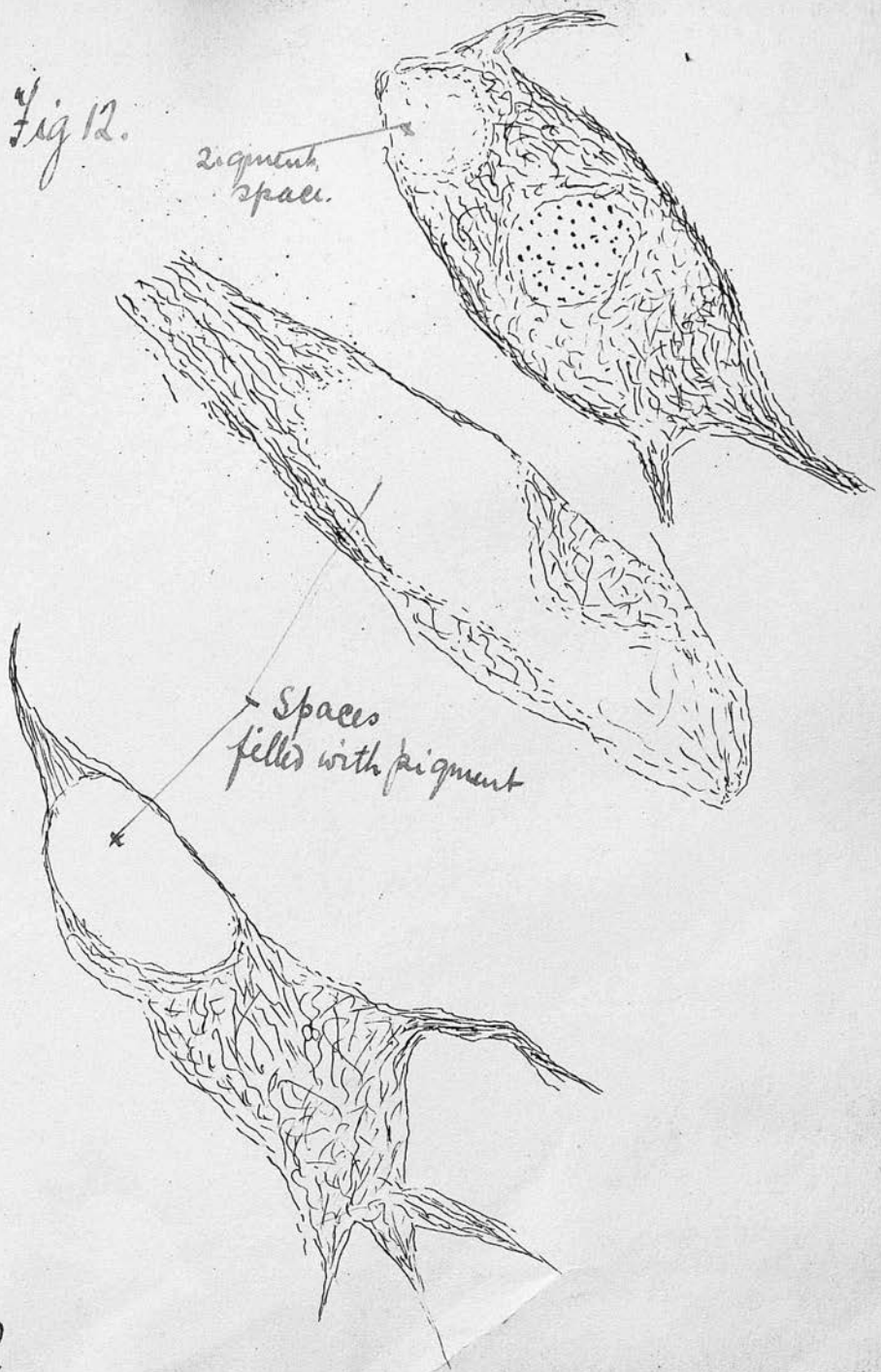


C.B.W.

Group of cells in various stages of degeneration;

Fig. 11.

Fig 12.



F.C.

A.F. General Paralysis

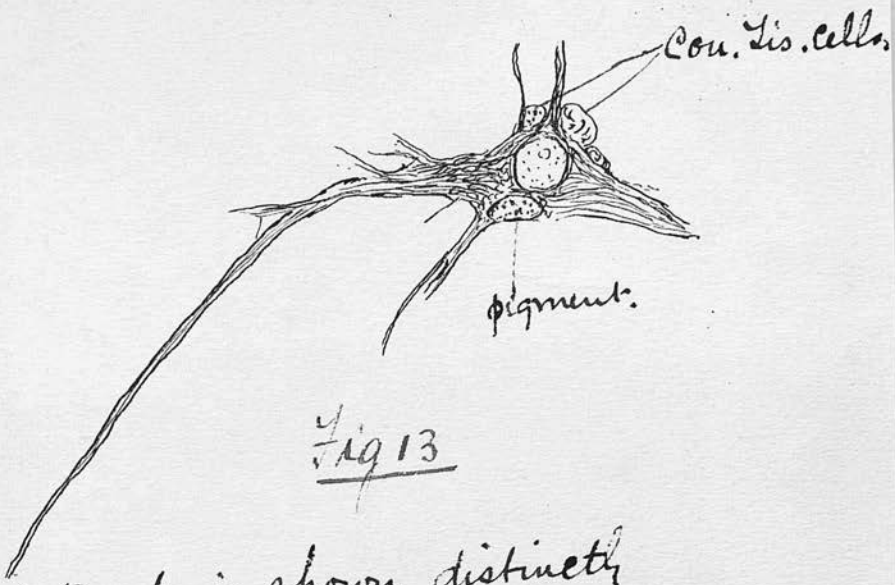
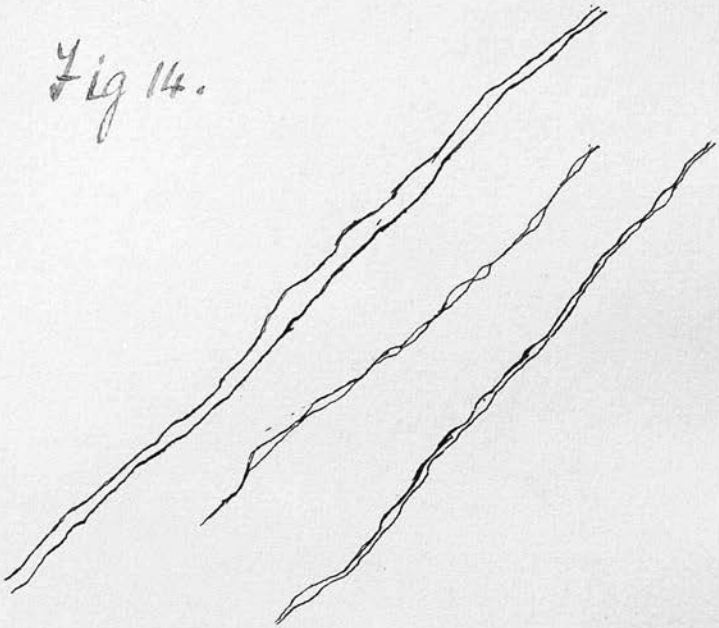


Fig 13

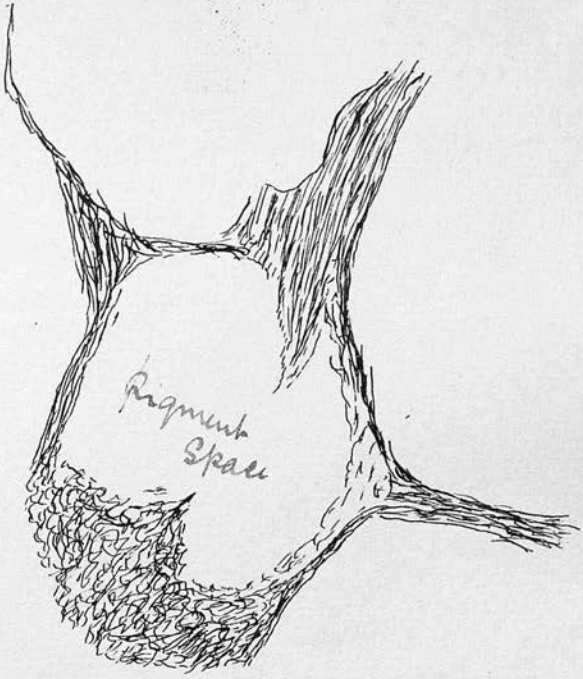
Network is shown distinctly
cell is shrunken and surrounded
by connective tissue cells (phagocytes)

The majority of the cells in this
Section are stunted, broken &
full of pigment.
(Early degeneration)

Fig 14.

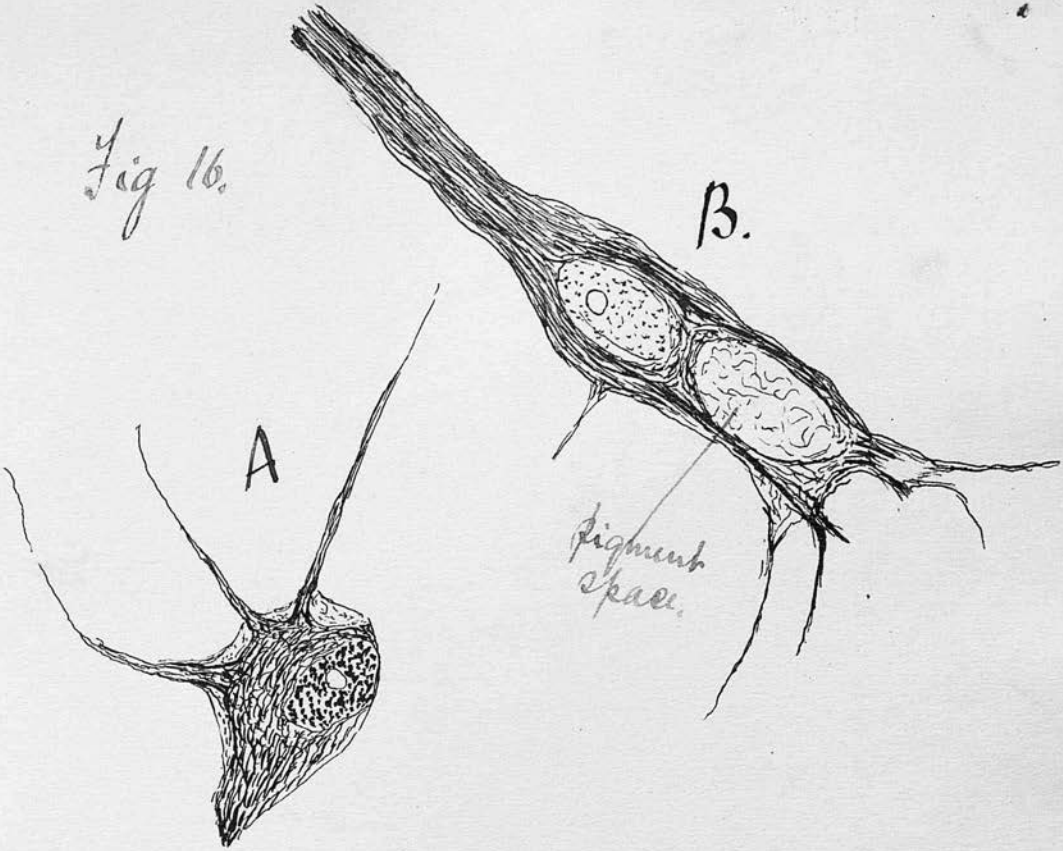


F.L.



M. A. O'B. Fig 15

Fig 16.

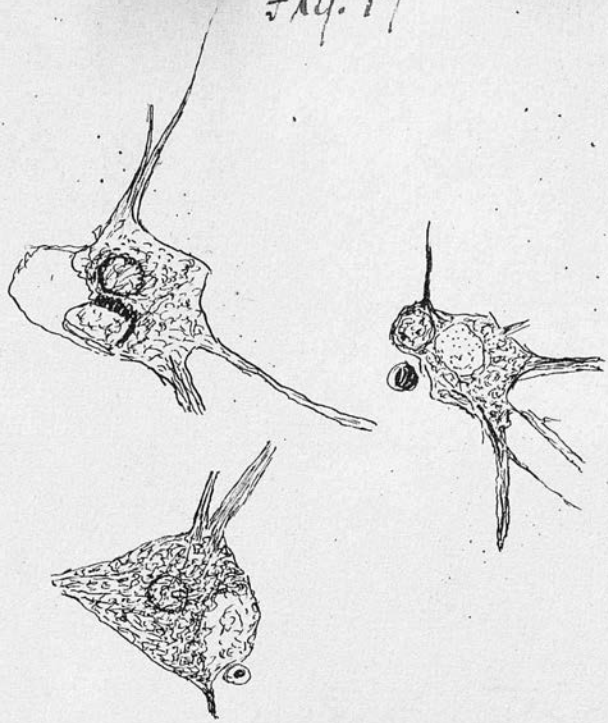


L.D.

Pericellular net.

C.L. drawing - Reitz 1/12 O.I.

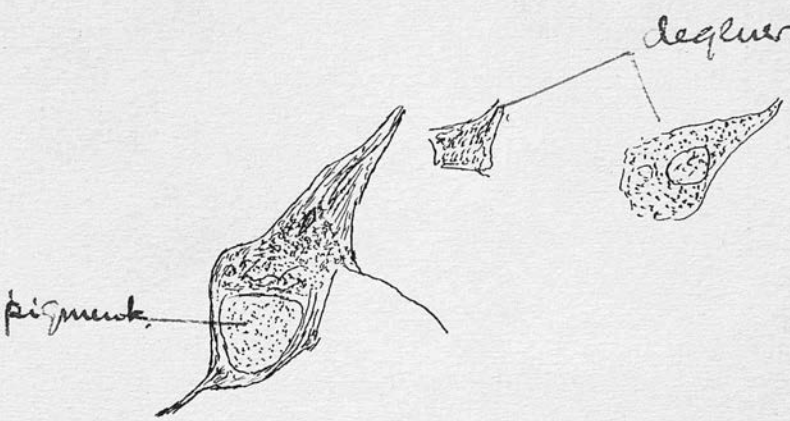
Fig. 14



S.D.

Cells from the ganglionic layer of the cortex. Endocellular network disintegrated, arrangement of fibrils indefinite, they are ~~better~~ more distinct in the processes: Each cell shows a large area occupied by yellow pigment.

Senile Dementia



E.A.T. The large ganglionic cells are marked pigmentary remains of network seen in typical process

Fig 18

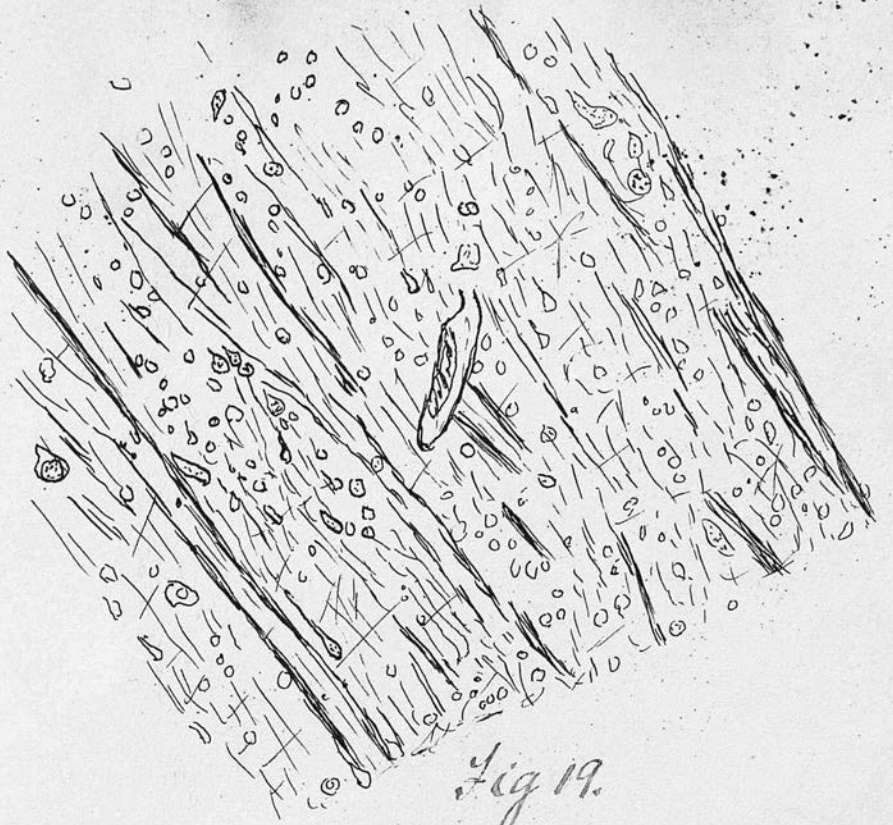
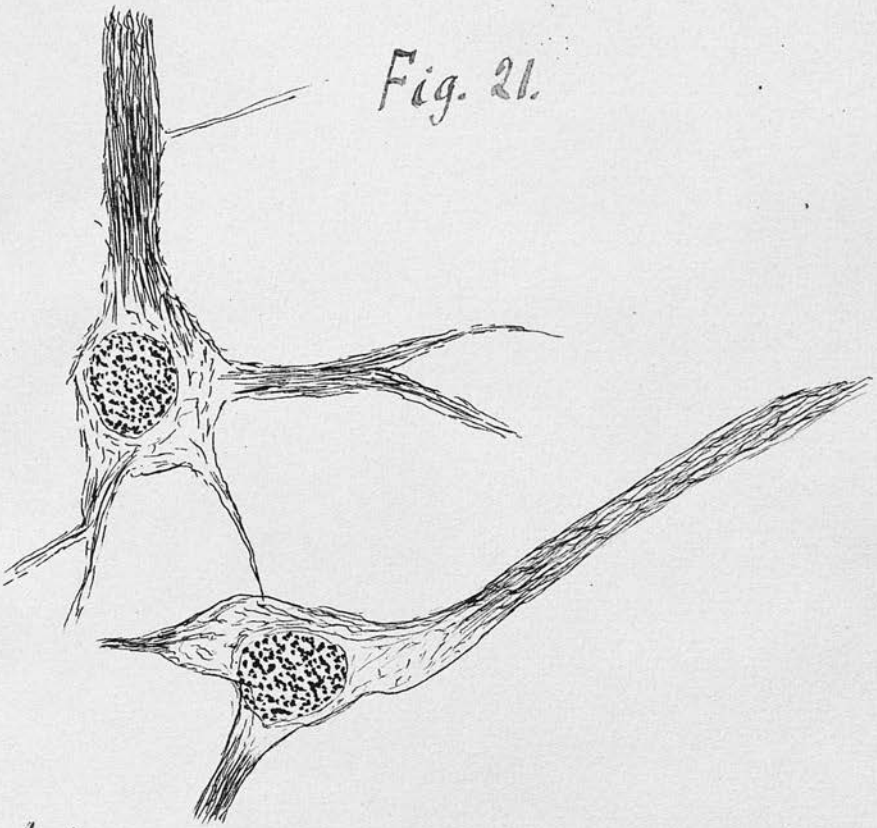


Fig 19.

I.K. Early degeneration-
Central intracellular condensation
looser meshwork at periphery
processes well preserved.

Fig 20

Fig. 21.



J. K.